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Brain Revealed

Handbook for Students and Practitioners

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TRAUMATIC BRAIN INJURIES

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Contents

1. General information

Traumatic brain injury involves an injury to the skull and brain parenchyma caused by mechanical force, most common in the case of falls, car accidents or assaults. Brain injury can be caused primary at time of trauma or secondary by the effect of intracranial hypertension triggered by trauma. More than half of the patients with coma in the emergency department still have more other organs injured. (2)

2. Clinical evaluation

Examination of the patient with craniocerebral trauma begins at the site of its occurrence. Includes: assessment of consciousness, blood

pressure, heart rate, aiming at ensuring the freedom of the airways, assessment of associated injuries. (12)

Associated with brain injury may be found lesions of the scalp or skull. Scalp injuries are important in providing information about the nature of the trauma. Skull lesions are classified as: *linear fractures, comminuted fractures, basal fractures. Linear fractures* are often produced in the neurocranium and are a sign of severe head injury. *Comminuted fractures* are of 2 types: inclusive and extrusive. May be associated with injuries of the dura mater. *Basal fractures* represent a danger through the possibility of creating a communication between the internal and external environment that can lead to posttraumatic meningitis. (19)

Posttraumatic brain injuries are also of several forms: *cerebral contusion, cerebral edema, shear axonal injuries, haemorrhage, ischemia, posttraumatic hydrocephalus.*

Cerebral contusions interest the nerve substance and vessels. Depending on the production mechanism can be direct or indirect. Direct contusions are produced by hitting the skull by an object which can lead to an adjacent lesion of the parenchyma. Indirect contusions are produced by deceleration mechanisms that lead to the collision of the parenchyma of bone structures on the opposite side of the trauma. Contusions can be single or multiple, focal or diffuse and can evolve if not treated correctly. There may be a correlation between the location of the contusions and the symptoms. (15)

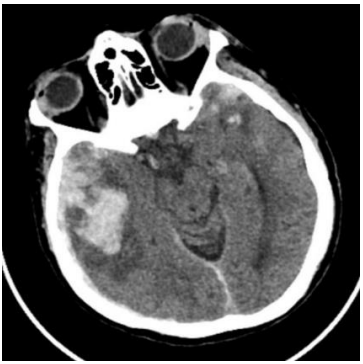

Figure 1. CT aspect of cerebral contusions
(Personal collection of dr. Vicențiu Săceleanu)

Cerebral edema is a way of responding to the parenchyma in case of trauma. It can be adjacent to a contusion or generalized to the entire surface of the brain.

Shear axonal injuries are very severe injuries with a poor prognosis. They are followed by sequelae, usually permanent. They are produced by the rotational movement of the cerebral hemispheres in the opposite direction, one to the other or both to the brainstem resulting in axonal damage.

Posttraumatic *haemorrhage* can take several forms: epidural, subdural, or intraparenchymal with or without ventricular burst.

Ischemia can be caused by the compressive effect of hematoma or cerebral edema.

Posttraumatic hydrocephalus is the accumulation of excess cerebrospinal fluid. It can occur acutely by obstructing the aqueduct with blood clots or later by hypersecretion of cerebrospinal fluid. (8)

Cranial nerve injuries are clinical features that can occur in the event of a brain injury. The mechanism of production can be a bone fracture that usually leads to acute and irreversible clinical signs or the compressive effect of cerebral edema, and the clinical signs appear later and are often reversible. (7)

Clinical signs that may occur in case of a brain trauma can be: headache, vertigo, vomiting, loss of consciousness. (6)

The most widely used consciousness assessment scale is the **Glasgow Coma Scale** which assesses the response to 3 samples resulting in the GCS score: (5)

1. Best eye opening:

- Spontaneous	4 points
- To speech	3 points
- To pain	2 points
- None	1 point

2. Best verbal:

- Oriented	5 points
- Confused	4 points
- Inappropriate	3 points
- Incomprehensible	2 points
- None	1 point

3. Best motor:

- Obeys	6 points
- Localizes pain	5 points
- Withdraws to pain	4 points
- Flexion (decorticate)	3 points
- Extensor (decerebrate)	2 points
- None	1 point

The MILLER classification divides brain injuries into 3 groups according to severity:

I. Minor traumatic brain injury – GCS: 13-15 p. Depending on the severity, it is subdivided into: grade 0 - without losing consciousness, the patient can go home; grade 0 with risk – (alcoholism, drugs, anticoagulant therapy, age, epilepsy), a CT scan should be performed and hospitalized is needed for 24 hours; grade 1 - loss of consciousness for up to 5 minutes, retrograde amnesia, persistent headache; grade 2 - loss of consciousness for 30 minutes.

II. Medium traumatic brain injury – GCS: 9-12 p. These patients require special attention, because they can worsen neurologically at any time.

III. Sever traumatic brain injury – GCS < 8 p., state of coma. (18)

In about 10-15% of cases of brain injuries are associated with injuries of other organs. (1)

3. Imaging evaluation

Skull radiography lost its importance with the use of brain CT as a routine examination as well as the usual use of bone window examination. May show cranial fractures, pneumocephalus, fluid level in the air sinuses, penetrating foreign bodies.

Cervical spine radiograph is performed in the case of patients with: GCS < 15, paresthesia in the upper limbs, focal neurological deficit, neck pain, failure to test neck movements, comatose patients, alcohol intoxication.

Cranial CT scan is indicated: in case of patients with GCS <14 p., state of coma, damage and / or neurological deficits, associated anticoagulant treatment, posttraumatic seizures, complex or

penetrating head wounds, suspected or confirmed CSF fistula. (4)

Patients with major brain trauma can perform cranial CT after stabilization of vital functions, and transportation will be performed under the supervision of the medical team. (11)

Signs that may appear on CT cranial scan:

- haemorrhage: epidural hematoma, subdural hematoma, subarachnoid haemorrhage, intraparenchymal haemorrhage, hemorrhagic contusion, ventricular haemorrhage
- hydrocephalus
- cerebral edema
- cranial fractures
- cerebral ischemia
- pneumocephalus
- midline shift

4. Pre-hospital treatment and patient transportation

The treatment of the patient with cerebral trauma begins with the first aid given at the scene of the incident. The main objectives are: ensuring vital functions, cervical rachis stabilization, evaluation of the level of consciousness, evaluation of associated injuries. (15)

The transport of the patient with minor cerebral trauma can be performed with any type of ambulance, while the patient with major cerebral trauma must be transported by ambulance with resuscitation equipment and emergency doctor to monitor vital functions. (1)

Treatment of wounds associated with brain trauma involves: shaving the hair around the wound about 2 cm, asepsis with betadine, anesthesia with lidocaine, debridement, suturing and again asepsis, application of a bandage that will be changed daily, tetanus prophylaxis, suppression of sutures after 6 -7 days. (16)

Minor traumatic brain injuries require: bed rest with the head raised to 30 degrees, symptomatic treatment for headache, vertigo, vomiting. (9)

Criteria for hospitalization:

- GCS 14 p. or less
- associated anticoagulant treatment or other risks

- amnesia over 5 minutes, vomiting, seizures, focal signs, positive CT (20)

Medium traumatic brain injuries require the same therapeutic recommendations as minor ones, with the addition of Mannitol for brain depletion in the case of anisocoria or focal motor deficits. (13)

It is necessary to monitor the neurological status and repeat the CT scan of the brain if the patient worsens neurologically. If GCS falls below 8 points, intubation is required. (20)

Patients with *major brain trauma* are in a coma and generally associate lesions of the facial mass, cervical spine, abdominal organs, etc. (3)

Increased attention will be paid to the prevention of cerebral side effects of deteriorated systemic factors (hypoxia, hypercarbia, anemia, hypotension). Stabilization of hemodynamics and respiration is mandatory. If an intracranial hematoma is detected by CT scan and has surgery indications, emergency surgery is performed. (17)

5. Extradural hematoma

Extradural hematoma is a collection of blood formed between the inner table and the dura mater. The cause of extradural hematoma is most commonly a post-traumatic arterial injury, in most cases of the middle meningeal artery. The most common location of the extradural hematoma is in the temporal region where the dura mater has minimal adhesion. The etiology of the hematoma can also be venous through the rupture of a venous sinus or in other cases can be due to skull fracture. (14)

Extradural hematoma mainly affects males and young people. Dura mater is more difficult to detach in infants and the elderly, which is why it is rare in these age groups. (20)

Symptomatology

The clinical course of extradural hematoma is staged. Initially there is a loss of consciousness, then there is a return to normal consciousness, then there are disorders of consciousness that progress to coma. In the absence of diagnosis and treatment, a contralateral motor deficit appears that progressively worsens, ipsilateral mydriasis and signs of decerebration. (9)

Paraclinical explorations

The cerebral CT examination is the examination of choice, highlighting the appearance of a spontaneously hyperdense biconvex lens, arranged immediately below the internal plate. Cerebral CT scan specifies the location which can be: temporal, frontal, parietal, occipital, bilateral or posterior fossa. (20)

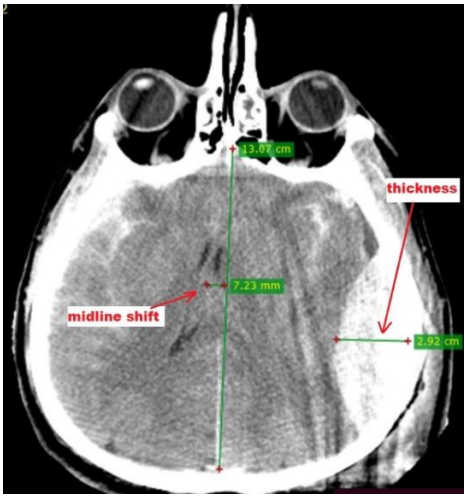

Figure 2. CT aspect of left convexital extradural hematoma (Personal collection of dr. Vicențiu Săceleanu)

Treatment

The treatment is surgical, the extradural hematoma representing a major neurosurgical emergency. The surgery treatment involves performing a bone flap centered on the hematoma, evacuating the hematoma, identifying the source of bleeding and hemostasis. (12)

Patients can be managed nonsurgically through serial CT scans if: volume < 30ml, thickness < 15mm, midline shift < 5mm, GCS >8p and no focal neurologic deficit.(9)

Overall mortality is about 5%. If the neurological signs are minor, postoperative healing is obtained in most cases. If there are signs of decerebration or peeling before the intervention, the mortality is 60-75%. (7)

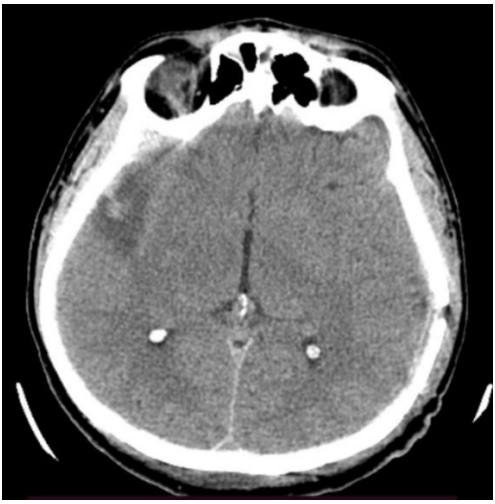

Figure 3. Postoperative CT aspect of right convexital epidural hematoma (Personal collection of dr. Vicențiu Săceleanu)

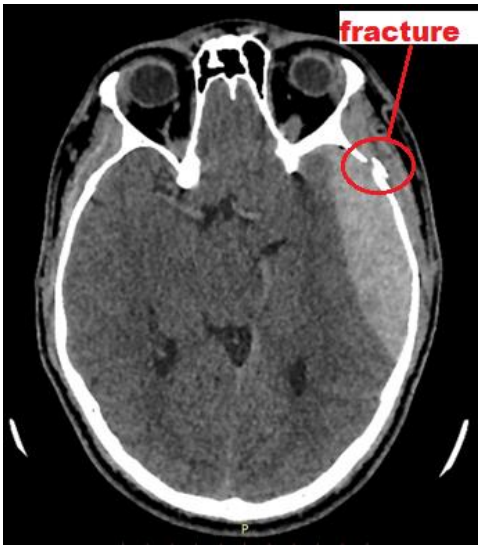

Figure 4. CT aspect of left fronto-temporal extradural hematoma associated with fracture skull fracture (Personal collection of dr. Vicențiu Săceleanu)

6. Acute Subdural hematoma

Acute subdural hematoma is a collection of blood between the dura mater and the brain. (14)

The cause is generally traumatic, the etiological substrate being the rupture of a vein, an artery or a cerebral dilaceration. (14)

Symptomatology

Clinical manifestations occur immediately post-traumatic. Most often, acute subdural hematoma is manifested by a brutally installed coma. Sometimes it copies the evolution of the extradural hematoma, with free interval, followed by disturbances of consciousness, contralateral deficit, ipsilateral mydriasis, coma and finally decerebration. Sometimes, acute subdural hematoma is relatively well tolerated, with the patient showing minimal signs of intracranial hypertension and minor disturbances of consciousness. (9)

Paraclinical explorations

Acute subdural hematoma appears in the form of a spontaneously hyperdense, hemispherically arranged collection, with poorly defined contours, located adjacent to the bone. Cranial CT examination detects hematoma volume, location, mass effect, and associated lesions. (20)

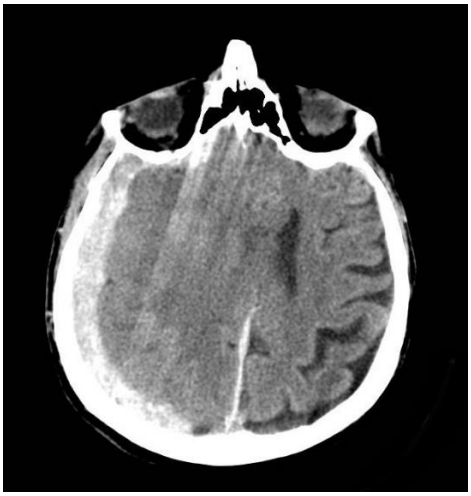

Figure 5. CT aspect of acute right subdural hematoma (Personal collection of dr. Vicențiu Săceleanu)

Treatment

Surgical treatment is performed urgently with the objectives of evacuating the hematoma, eliminating the compressive effect on the brain and hemostasis. (15)

Surgical indications is based on CT appearance and clinical signs:

- Thickness of hematoma > 10 mm, or midline shift > 5 mm – surgery is indicated irrespective of GCS

- Thickness < 10 mm, shift < 5 mm - surgery is performed if: GCS decreases by 2 points, anisocoria, intracranial pressure>20mmHg.

The surgery involves performing a bone flap centered on the lesion, large enough to allow cerebral decompression or for a possible decompressive craniectomy if necessary.

The prognosis is reserved, mortality being 50-75%, and healing with postoperative sequelae 60%. (14)

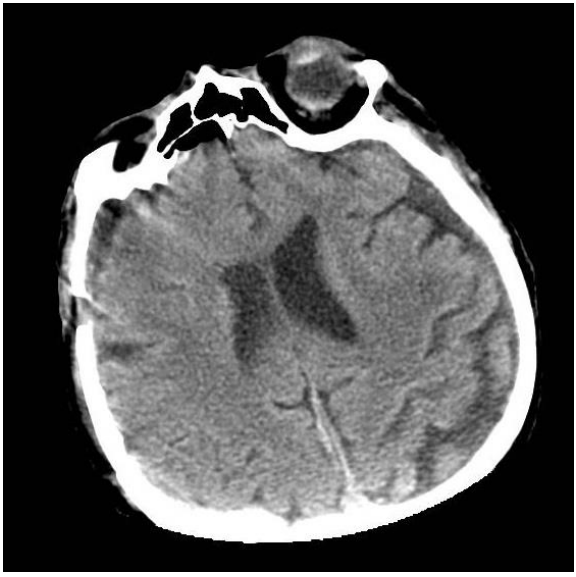

Figure 6. Postoperative aspect of acute subdural convexital right hematoma
(Personal collection of dr. Vicențiu Săceleanu)

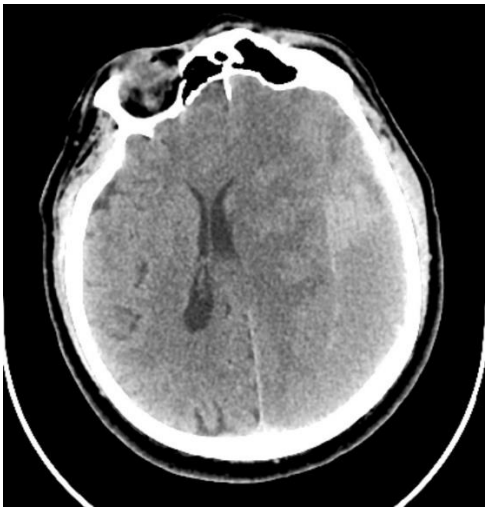

Figure 7. CT aspect of subacute left convexital subdural hematoma (Personal collection of dr. Vicențiu Săceleanu)

7. Chronic subdural hematoma

Chronic subdural hematoma is a blood collection between the dura mater and the brain.

Chronic subdural hematoma develops slowly over several weeks, sometimes months, as a result of an unnoticed minor brain trauma. Affects extreme ages: newborn, toddler and the elderly.

The source of blood may be the rupture of a corticodural vessel. They are in tension in case of a cortical atrophy which increases the predisposition to rupture of the vessel. (14)

Symptomatology

Symptoms appear progressively over the course of weeks. The patient may have: headache, motor deficit, speech disorders, behavioral disorders. (9)

Paraclinical explorations

The cranial CT scan is the quick, elective investigation that allows the assessment of the location, volume and mass effect produced by the hematoma. The imaging aspect is of isodense collection at the beginning, which later becomes hypodense. A heterogeneous

hyperdensity in this collection indicates a recent bleeding. Contrast injection loads the contours of the hematoma membrane. (12)

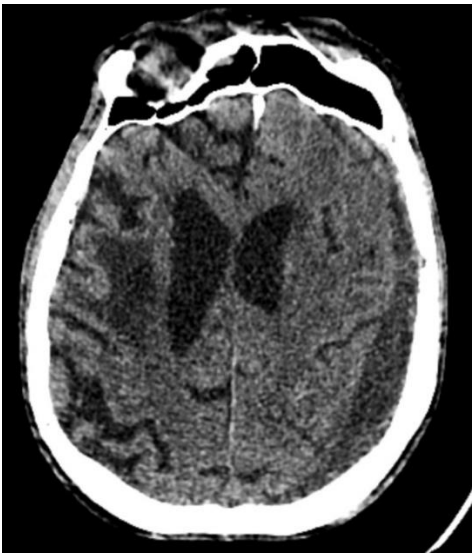

Figure 8. CT aspect of chronic subdural convexital left hematoma (Personal collection of dr. Vicențiu Săceleanu)

Treatment

In chronic subdural hematomas, the therapeutic attitude is correlated with the clinical picture and the appearance of the brain CT. Chronic low volume subdural hematomas are generally poor in symptoms. Surgical abstinence, clinical surveillance and CT re-examination are preferred.

Surgical treatment is indicated when the hematoma is over 1 cm thick and produces symptoms.

The most commonly used surgical technique is craniectomy through a drill hole and draining the hematoma for 48 hours to prevent bleeding and accumulation of air in the remaining cavity.

The prognosis is generally good with improving the patient's neurological condition. (16)

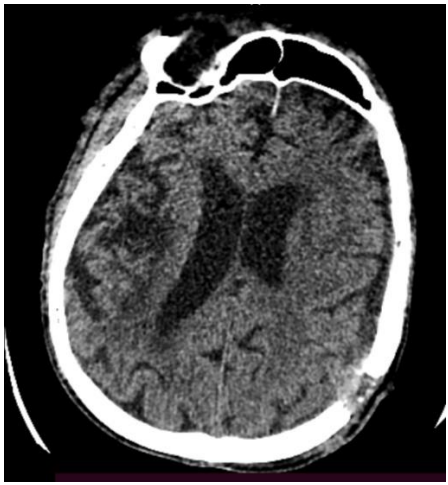

Figure 9. Postoperative CT aspect of chronic convexital left hematoma (Personal collection of dr. Vicențiu Săceleanu)

8. Posttraumatic intraparenchymal hematoma

It is a blood collection in the brain parenchyma acquired post-traumatic due to a contusion or a laceration. They occur mainly in the frontal and temporal lobes. During evolution, it can grow and open the subdural space or ventricles or it can resorb on its own. (16)

Symptomatology

Symptoms include: signs of intracranial hypertension, altered consciousness.

Paraclinical explorations

Cranial CT detects an intraparenchymal hyperdensity, possibly corticalized. Perilesional appears as a hypodense halo that represents edema. It has a mass effect on the brain parenchyma. Subdural or epidural hemorrhages may also occur in other regions. (5)

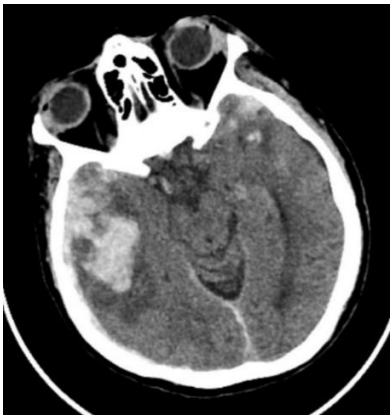

Figure 10. CT aspect of cerebral frontal right intraparenchymal hematoma (Personal collection of dr. Vicențiu Săceleanu)

Treatment

Surgical treatment is performed if the volume of the hematoma is large and aggravates the neurological condition of the patient or if no clinical response is obtained by drug treatment. If the hematoma increases in size, imaging and neurological reassessment in dynamics is recommended. (18)

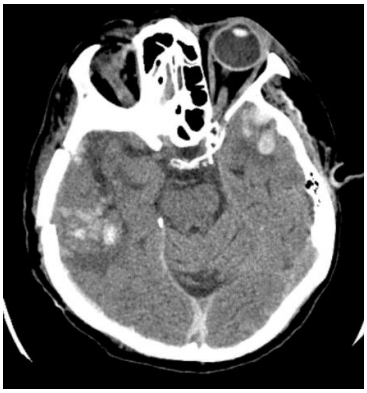

Figure 11. Postoperative CT aspect of cerebral frontal right intraparenchymal hematoma (Personal collection of dr. Vicențiu Săceleanu)

9. Skull fractures

Skull fractures can be classified into simple or compound fractures. Linear fractures of convexity rarely require surgery. Surgery is indicated in cranial fractures in which the depression of a bone fragment is greater than the thickness of the bone in that region. (10)

The purpose of the intervention is to perform hemostasis in the fracture site that can lead to an extradural hematoma, to remove the bone fragment migrated to the parenchyma and any foreign bodies. (4)

Nonsurgical treatment is applied if the depression of the bone fragment is less than 1 cm, there are no clinical or imagistic signs of dural penetration, no sinus is involved, no infected wounds are associated. Closed skull fractures and base skull fractures have no surgery indication. (15)

In the case of craniocerebral trauma, the so-called traumatic approach must be considered. The principles of this approach are:

- the patient positioned in supine position with the head rotated contralateral to the lesion and elevated to 15-30 degrees;
- the skin incision is made in the form of a question mark (or a question mark turned over in the right-side approach). It starts at the level of the zygomatic arch, 1 cm anterior to the tragus continues superiorly and then posteriorly enveloping the auricular pavilion. After reaching the back of the auricular pavilion, it follows a higher path to the paramedian level, after which it curves forward and ends at the hairline;
- a burr hole is made in the sphenoid bone depression, the rest of burr holes are made along the edge of the incision;
- the dura mater is then incised and suspended;
- if a decompressive craniectomy is considered, the flap will not be repositioned. It will attach in a second operator time. (12)

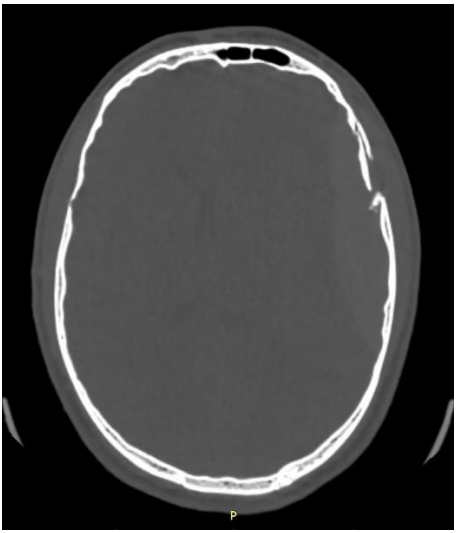

Figure 12. CT aspect of left frontal skull fracture
(Personal collection of dr. Vicențiu Săceleanu)

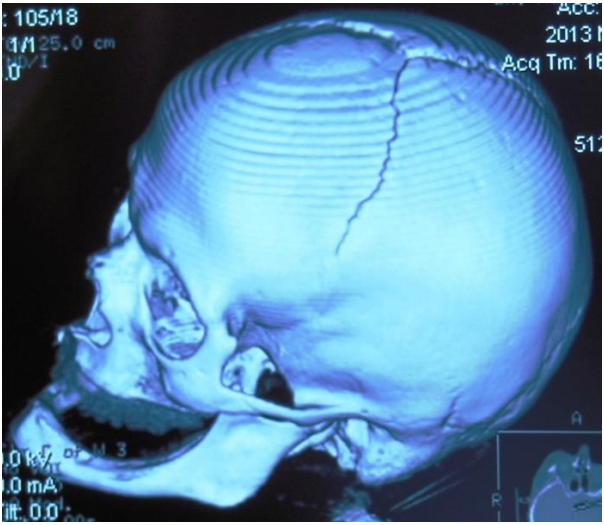

Figure 13. 3D CT aspect of left parietal fracture
(Personal collection of dr. Vicențiu Săceleanu)

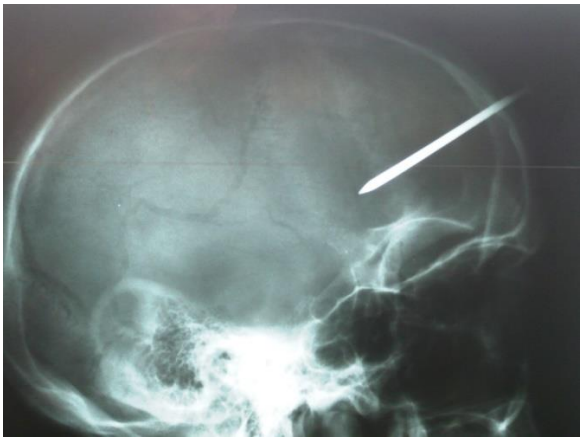

Figure 14. Skull fracture caused by foreign body penetration (Personal collection of dr. Vicențiu Săceleanu)

10. Scalp lesions

Scalp lesions can be represented by: swelling, bruising or even wounds. All this represents the traumatic mark. It is important in providing information about how the brain trauma occurred.

Depending on their appearance, they can be linear, stellate or with lack of substance.

Depending on the production mechanism they can be: wounds by cutting, wounds by concussion (produced by crushing a solid plane), wounds by shooting. (12)

Figure 15. Occipital linear wound
(Personal collection of dr. Vicențiu Săceleanu)

Figure 16. Deep paramedian frontal wound
(Personal collection of dr. Vicențiu Săceleanu)

Wound treatment should follow the steps:

- shaving the hair 2 cm around the wound;
- wound inspection for any foreign bodies or bone fragments;
- cleaning and asepsis of the wound with hydrogen peroxide, saline, betadine solution;
- excision of devitalized areas;
- wound suture;
- a new asepsis of the wound and the application of a sterile dressing;
- tetanus prophylaxis and antibiotic therapy;
- wound dressing and asepsis will be performed once every 2 days; and at 8-10 days the sutures will be suppressed. (15)

Disclaimer: *The authors have no conflicts of interest to declare.*

References:

1. Andrews, B. T. (2003). *Intensive Care in Neurosurgery.* Thieme.
2. Anzai, Y. (2015). *Imaging of Traumatic Brain Injury.*
3. Bor-Seng-Shu E, F. E. (n.d.). *Decompressive craniectomy: a meta-analysis of influences on intracranial pressure and cerebral perfusion pressure in the treatment of traumatic brain injury. .* 2012.
4. Connoly, E. S. (2010). *Fundamental Operative Techniques in Neurosurgery.* Thieme.
5. Greenberg, M. S. (2020). *Handbook of Neurosurgery.*
6. Haines, S. J., & Walters, B. C. (2006). *Evidence-Based Neurosurgery.* Thieme.
7. Heydari F, G. M. (2019). *Traumatic Brain Injury in Older Adults Presenting to the Emergency Department: Epidemiology, Outcomes and Risk Factors Predicting the Prognosis.*
8. Iki Y, M. Y. (n.d.). *Traumatic Middle Meningeal Arteriovenous Fistula of Non-fractured Site Detected by Four-dimensional Computed Tomography.* 2020.
9. Jong's, D. (2013). *The Neurologic Examiantion.*
10. Khurram A, K. T. (2014). *Clinical associations and causes of convexity subarachnoid hemorrhage.*
11. Kulesza B, L. J. (2020). *Initial factors Affecting 6 monthsOutcome of Patients Undergoind Surgery for Acute Post traumatic Subdural and Epidural Hematoma.*
12. Louts, C. (n.d.). *Neurosurgery Emergencies.* Thieme.

13. LT., D. (2002). *Raised intracranial pressure. J Neurol Neurosurg Psychiatry.*
14. Marcolini E, H. J. (n.d.). *Approach to the Diagnosis and Management of Subarachnoid Hemorrhage.* 2019: West J Emerg Med.
15. Saceleanu, V. (2014). *Clinical Neurosurgery.*
16. Schmidek. (n.d.). *Operative Neurosurgical Techniques.*
17. Schuenke, M. (n.d.). *Atlas of Anatomy Head and Neuroanatomy.* 2010.
18. Sindou, M. (2009). *Practical Handbook of Neurosurgery.*
19. Thamburaj, V. A. (n.d.). *Textbook of contemporary Neurosurgery.*
20. Ullman, J. S. (2015). *Atlas of Emergency Neurosurgery.* Thieme.

ISCHEMIC STROKE

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Contents

1. Definitions

The ischemic stroke pathology resides on three distinguishable concepts: the transient ischaemic attack, the stroke and the watershed infarct.

Stroke or cerebral infarction is an irreversible death of brain tissue due to inadequate or absence blood flow perfusion in a region of the brain or brainstem.

Transient ischaemic attack is a temporary dysfunction that occurs secondary to a focal ischaemia without acute infarction or permanent stroke.

Watershed infarction is an ischaemic infarction that occurs in a peripheral region served by two isolated arterial branches caused by a

disturbance in blood perfusion in one or both arteries.

In all cases, decrease of cerebral blood flow may occur through an occlusion or an arterial spasm. Arterial occlusion may be thrombotic or embolic.

2. Epidemiology

Ischemic and hemorrhagic strokes represent together the third cause of death after heart diseases and neoplasms. The annual mortality from this condition varies in Europe between 64-274/100.000 inhabitants.

CI represents the largest proportion (70-80%) of total strokes. Around 50% of CI are due to the atherosclerotic disease of the large vessels. Another 20% are produced by lacunar infarctions due to the occlusion of the penetrating deep arteries with low diameter. Embolic events are the source of 30% of CI, the most frequent starting point being the cardiac source.

3. Etiology

By far, the first cause of ischaemic and hemorrhagic stroke is **atherosclerosis** of arteries occurring especially in the elder population.

The second cause of ischaemic stroke is embolia. This condition occurs especially in the population with cardiac comorbidities such as atrial fibrillation, cardiomyopathy, myocardial infarction, rheumatic heart disease, mitral valve prolapse or endocarditis and in the population of patients with aorta arch conditions such as atherosclerosis with a wall thickness greater than 4 mm.

Other causes consists of clotting disorders such as protein deficiencies of C, S, AT III or thrombophilia, autoimmune or infectious vasculitis, administration of oral contraceptives, cerebral thrombophlebitis, radiotherapy, non-inflammatory vasculopathies such as carotid or vertebral artery dissections, moyamoya disease, pseudoxanthoma elasticum, homocystinuria or fibromuscular dysplasia, vasculopathies such as Takayasu's, infectious: TB, syphilis, ophthalmic zoster, amphetamine abuse and miscellaneous causes such as idiopathic, cerebral venous thrombosis, migraine, cocaine abuse or posterior reversible encephalopathy syndrome.

4. Risk factors

The most important factors of ischaemic stroke that facilitate also the apparition of atherosclerosis are modifiable risk factors in relation to lifestyle such as smoking, animal fat enriched diet, excessive intake of alcohol and/or coffee, stress and sedentarism and modifiable risk factors in relation to some pathologies, such as arterial hypertension, type 2 diabetes, hiperlipidemias, obesity and oral contraceptives administration. The non modifiable factors that increase the risk of ischaemic stroke are the age of patients, the gender and personality.

Smoking. A smoker's risk of suffering cardiovascular disease is twice more frequently than in nonsmokers. Nicotine infusion in blood causes arteriolar vasoconstriction, tachycardia, intensifies myocardial activity consequently increasing the arterial blood pressure.

Alcohol. High intake leads to obesity and dyslipidemia, in addition to the occurrence of chronic gastritis, peptic ulcers, liver disease, pancreatic and polyneuropathy.

Coffee. Increasing the amount of more than two cups of coffee / day causes tachycardia, hypertension and favours the occurrence of heart rhythm disorders.

Blood pressure. The guidelines developed by the World Health Organization and the International Society of Hypertension (1999) defines hypertension as a systolic pressure of 140 mm Hg or higher and / or diastolic blood pressure of 90 mm Hg or greater, in the people who receive no kind of antihypertensive medication. The values apply to people over 18 years old.

Diabetes accelerates the accumulation of cholesterol deposits in vascular walls, favouring the emergence and progression of atherosclerosis.

Dyslipidemia is the appearance of an imbalance in the normal concentrations of serum lipids. Hypercholesterolemia occurs either due to a cholesterol-rich diet or by its excessive production in the liver due to hereditary abnormalities.

Obesity is the increased body mass index (BMI) over 30.

5. Pathogenesis

In the stroke pathogenesis the following mechanisms are implied such as the **intrinsic processes to the atrial wall** that comprise atherosclerotic formation of atheroma plaque, lipohyalinosis, inflammatory lesions and arterial dissection.

The occurrence of a laceration in the intima of the arterial wall (in particular, at the level of the atheroma plaque with anfractuous edges) causes blood to come into contact with the subintimal tissue (especially with the collagen) consequently occurring the phenomenon of platelet adhesion. The platelets adhesion to the vascular wall undergo a series of biochemical reactions that result in the release of coagulation factors which produce the phenomenon of platelet aggregation. In their turn, the aggregated platelets release substances that are the origin of other platelet aggregation, causing a chain reaction. The result of this chain reaction is the formation of the white thrombus (platelet). It may break, resulting in the appearance of platelet emboli. To this white thrombus, a number of substances contained in the blood and especially in fibrin filaments adhere. They form a network (like a net) of red blood cells resulting over time in the red thrombus because of the inward wall stagnation. The red thrombus can evolve in three ways, it may gradually increase and cause vessel occlusion, it can detach partially or totally within bloodstream and thereby constitute an embolism or it may undergo a local transformation that will result in its local coverage from the intimate and inclusion into the atrial wall. This phenomenon results in the appearance of a non-evolving stenosed scar at wall level and the production of blood hemodynamic changes.

Another pathogenic mechanism is the ***cardiac embolism*** from a high caliber extracranial vessel (aortic arch, carotid and vertebral arteries) to low caliber intracranial vessel and by far, the most important mechanism is **reduction of perfusion pressure** that can occur through hypotension in patients with atherosclerosis. Another mechanism is **rupture of a cerebral vessel** with secondary spasm and subsequent ischemia (e.g. in subarachnoid hemorrhage SAH) and the last mechanism consists in the **hemodynamic mechanism**. Blood steal syndrome occurs more frequently in the subclavian steal syndrome, that

consists in the subclavian artery occlusion proximally to the origin of the vertebral artery.

Whatever the mechanism be incriminated in the production of ischaemic stroke, after the removal of blood supply due to obstruction or the brain blood vessels hypoperfusion, within a few minutes, in that region will occur the death of the nerve cells.

The area around this centre is called ischemic penumbra and contains functionally damaged brain tissue but still viable due to the blood supply through the collateral vessels. If ischemia remains in this reversible damaged area, the central area can be included soon, which is already infarcted, leading to the progressive increase of brain damage. The therapeutic strategies aimed are limiting the area of ischemic penumbra.

6. Clinical picture

Clinical picture severity in cerebral ischemia depends on the size and location of the embolus, on the alternative possibilities of collateral circulation. This collateral circulation may be localized between the territories of ICA and ECA through branches of the middle cerebral artery (MCA) with facial artery and internal maxillary artery or between the internal carotid artery (ICA) and the posterior cerebral artery, through the circle of Willis at the base of the brain.

A very important diagnostic tool in recognizing the symptoms of a stroke consists in the clinical observation of the medical practitioner of the clinical findings on the patient that presents in the emergency department, like the rapidly instalment of hemi or monoparesis, sometimes impaired consciousness, brutal or mild headache, the sudden loss of vision in one eye (amaurosis fugax), both eyes, or half of the visual field (hemianopsie), or the occurrence of double vision, aphasia, dysarthria, ataxia, balance disorders, muscular fatigability in the extremities and or loss of sensitivity on a limb or limbs.

7. Vascular syndromes

The most important vascular syndromes consists of the symptomes given by the occlusion of the arteries that perfuse that respective area. There are five major syndromes: the anterior choroidal artery syndrome

that has clinically sensoriomotor hemiparesis, the anterior cerebral artery syndrome that gives hemiparesis with predominance of crural motor deficit, urinary incontinence and frontal lobe syndrome in bilateral obstruction, middle cerebral artery that gives contralateral sensorimotor deficits, hemianopsie, lateral deviation of the head and eyes towards the brain injury, in the damaged dominant hemisphere-aphasia, posterior cerebral artery syndrome that gives hemianopsie and sometimes smooth-receptive aphasia when the dominant hemisphere is damaged and the basilar or vertebral artery syndrome that traduces in visual field disorders, ataxia, vertigo, dysarthria, dysphagia, ocular motility impairment, loss of consciousness, hemihypoesthesia and equilibrium impairment.

8. Evaluation

First of all, the patient must be assessed on the history and physical exam that will elude the clinician in discovering the systemic disease and the modifiable or non-modifiable factors that contributed to the apparition of the pathology. So, in order to assess the risk factors first as a clinician you must maintain a good knowledge of cardiology work-up including the ECG and echocardiography. The bloodwork assessment must include routine electrolytes, CBC, platelet count, coagulation parameters and VDRL and for unexplained stroke: ANA, AT III, protein C, protein S, homocysteine, Leiden factor, toxicology screening.

Other miscellaneous tests include U/A, CXR or when indicated, CSF exam.

As for the imagistic assessment you can perform a CT-scan for rapid evaluation or the not so necessary investigation of angiography (this investigation may occasionally assess cerebral embolism if performed within 48 hours of onset).

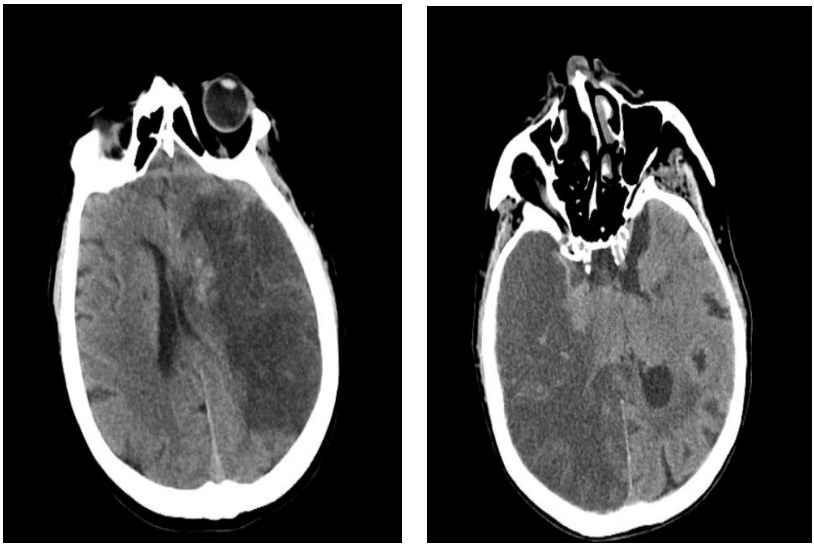

Figure 1. These images are showing two different patients that had an ischaemic stroke (total sylvian stroke) which should undergo surgery. (Personal collection of dr. Vicențiu Săceleanu)

9. Medicamentous treatment

There are several pillars that you need to assess in order to treat efficiently a patient that presents a stroke.

The first one is stabilizing the arterial blood pressure by administering antihypertensive medication. The next step is assessing the temperature by stabilizing it at a value lower than 38 degrees Celsius and controlling the level of blood glucose.

Another very important pylon in assessing a proper treatment is inducing a normal thrombolysis based on the tissue plasminogen activator that is administered within 3 hours from the onset of stroke, after the CT scan, which will exclude a cerebral hemorrhage. Thrombolysis is contraindicated when blood pressure is higher than 185/110 mmHg or if the patient has suffered from a cerebral, gastrointestinal or urological hemorrhage in the last 3 weeks. The dose is 0,9 mg/kg body intravenous, 10% in bolus and the rest of it after 1 hour, maximum 90 mg.

In order to maintain a good hemodinamic state the clinician needs to assess an INR of 2.3 to 3.5 in a cardiac embolism, carotid, vertebral dissection by inducing heparinization and anticoagulant therapy. In transient ischaemic attack or atherosclerotic thrombotic infarction antiplatelet therapy must be administered, like aspirin, ticlopidine or clopidogrel.

If cerebral edema is present, then specific treatment is mandatory with Mannitol 20 % in the first 3-5 days (pev).

Secondary prophylaxis is assessed with antiplatelet agents like aspirin, clopidogrel or ticagrelor, anticoagulants like warfarin maintaining an INR at 2-3, statins for the stabilization of the atheroma plaques and vascular endothelial remodelling, endovascular surgery in symptomatic carotid stenosis with a lumen narrowing greater than 70 %, treatment for risk factors like hypertension, type II diabetes, dyslipidemia, smoking or alcohol, neuroprotectors and physical therapy for early mobilization of patients.

10. Surgical treatment

One should distinguish between primary hemorrhage in which the initial event is the vascular rupture, from the hemorrhagic transformation, the latter appearing as a complication of the ischemic stroke, being developed inside the ischemic area, being produced through vascular occlusion, produced spontaneously or induced by the thrombotic or anticoagulant therapy. The differentiation is necessary in order to establish etiology and treatment, which are totally different. This is a common complication in infarctions consecutive to cerebral embolism (50-70%) compared with post-thrombotic infarction (2-20%). The time-window for the conversion to hemorrhagic stroke from an ischaemic one is about 3-7 days. Hemorrhagic transformation is conditioned by the reperfusion of the infarcted area. There are two types of hemorrhagic transformation: hemorrhagic transformation in the periphery, mostly interesting the gray matter, the most frequent situation and rupture of an artery in the central infarcted area, the incident taking the appearance of a hematoma (at the CT examination). The last one occurs very rarely.

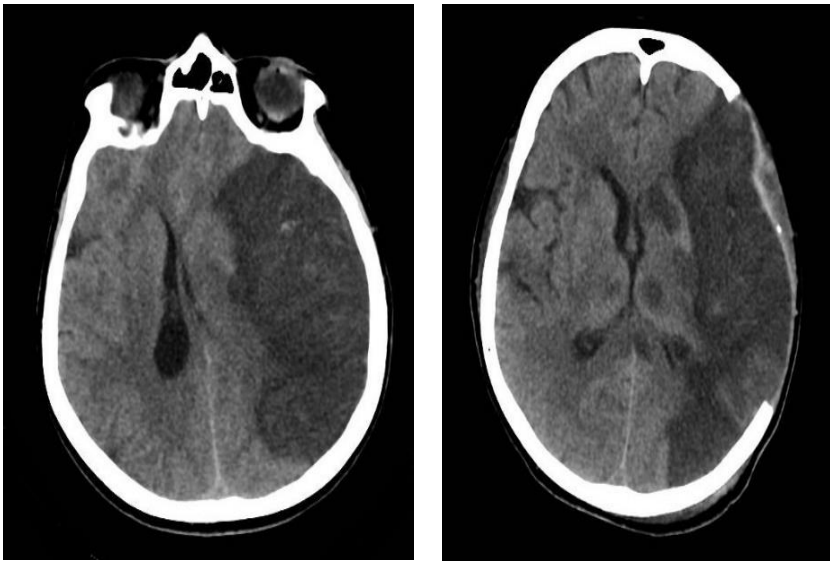

*Figure **2.** The left image shows a preoperatory sylvian ischaemic stroke and the right image exemplifies the postoperatory management of the stroke. (Personal collection of dr. Vicențiu Săceleanu)*

The hemorrhagic transformation can be assessed both clinically and radiologically comprising a large spectrum of secondary bleeding ranging from small areas of spot hemorrhage to intraparenchymal hematoma. More than half of all cerebral infarcts develop at some point a hemorrhagic component, although most (89%) are petechial hemorrhages, and the minority (11%) are forming hematomas.

From a clinical point of view, the hemorrhagic transformation of the ischemic stroke may be symptomatic and asymptomatic, manifested by a rapid deterioration of the patient normal state resulting in signs of intracranial hypertension with marked headache, nausea and vomiting and altered consciousness up to coma.

The surgical intervention should be performed before the occurrence of brainstem lesions and as early as possible, taking advantage of the "window" offered by the administration of cerebral antiedematous medication. Another decisive factor in deciding upon the surgical intervention is the biological status of the patient before the

onset of stroke. Patients under 60 are the ideal candidates, as well as those with minimal associated conditions. Surgical intervention can be performed even when TPA is administered. The operative technique consists in performing a decompressive hemicraniectomy in order to get as much functional independence of the patient. Cranioplasty can be made after three months if there are no signs of local infection.

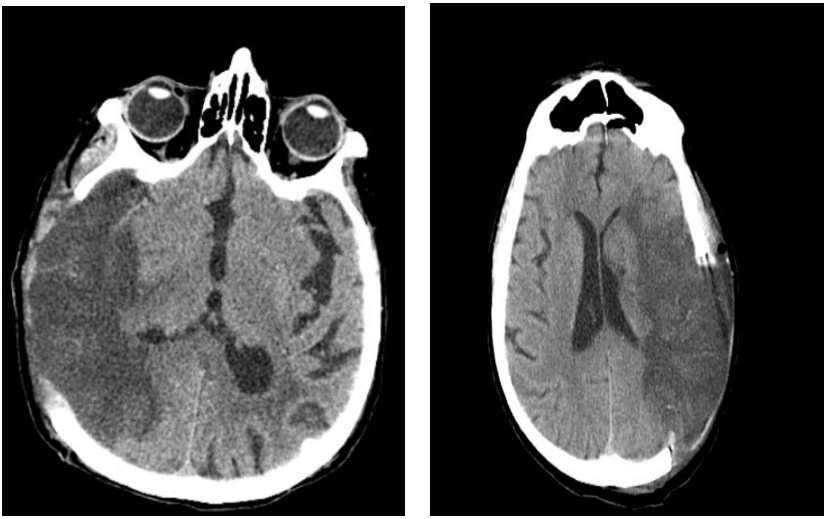

*Figure **3.** These images are showing the same two patients that had undergone the surgery (decompressive craniectomy). (Personal collection of dr. Vicențiu Săceleanu).*

Follow-up

Medical rehabilitation is very important and aims to enable people with neurological sequelae to achieve and maintain optimal physical, intellectual, psychological, social functions. Recovery begins in the first days after the onset. The recommended methods are physiotherapy, occupational therapy, speech therapy.

***Disclaimer:** The authors have no conflicts of interest to declare.*

References:

1. Adam D. Compendiu de neurotraumatologie, Editura didactică şi pedagogică, Bucureşti. 2009.
2. Adams HP, Brott TG, Crowell RM, Furlan AJ, Gomez CR. Guidelines for the Management of Patients with Acute Ischemic Stroke, 1994.
3. Arseni C. Boli vasculare ale creierului, vol 2, partea a II-a, Ed. Academiei Române, Bucureşti, 1984.
4. Arseni C. Tratat de Neurologie, Edit. Medicală, 1982.
5. Arseni C, Popoviciu L. Semiologie neurologică, Edit.Didactică și Pedagogică, București, 1983.
6. Băjenaru O. Ghid de diagnostic si tratement în neurologie, 2010.
7. Bor-Seng-Shu E, Figueiredo EG, Amorim RLO, Teixeira MJ, Valbuza JS, de Oliveira MM, et al. Decompressive craniectomy: a meta-analysis of influences on intracranial pressure and cerebral perfusion pressure in the treatment of traumatic brain injury. A review. J Neurosurg 117:589–596, 2012.
8. Borstein NM, Chemmanam T, Davis S. Stroke, Basel, Karger, 2009; 174-175.
9. Bulboacă A. Patogeneza accidentului vascular cerebral ischemic, Ed. Echinox, 2003
10. Ciurea AV, Constantinovici A. Ghid practic de Neurochirurgie, Edit.Medicală, 1988.
11. Ciurea AV. Patologia neurochirurgicală. Tratat de patologie chirurgicală, sub red.N. Angelescu, Vol. II, Edit. Medicală, Craiova, 2001.
12. Ciurea AV, Iacob G. Tehnici neurochirurgicale, Edit. Cartea Universitară, București, 2006.
13. Ciurea AV. Tratat de Neurochirurgie, vol. 1, Edit. Medicală, București, 2010.
14. Ciurea AV. Tratat de Neurochirurgie, vol.2, Edit. Medicală, București, 2011.
15. Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk AM, Hill MD, Patronas N, Latour L, Warach S. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet 2007; 369: 293-298.
16. Florian I St. Neurochirurgie. Curs pentru studenți, Cluj-Napoca, Edit.Srima, 2003.
17. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a guideline for health care professionals from the American Heart Association/American Stroke Association. Stroke. Feb 2011; 42(2): 517-84.

18. Goldstein LB, Simel DL. Is this patient having a stroke? JAMA 2005; 293: 2391-2402.
19. Gorgan RM. Ghid în patologia neurochirurgicală, Editura didactică și pedagogică, București, 2008.
20. Greenberg MS. Handbook of Neurosurgery, Thieme, Medical Publishers, New York, 2020.
21. Gupta R, Connolly ES, Mayer S, Elkind MSV. Hemicraniectomy for massive middle cerebral artery territory infarction: a systematic review. Stroke 35:539–543, 2004.
22. Hachinsky VC. Advances in Stroke 2002: introduction, Stroke, 2003, 34:323.
23. Ienceanu StM. Actual state in intracranial hipertension, Edit. Gh.Asachi, Iași, 2003.
24. Ienceanu ȘtM, Ciurea AV. Hipertensiunea intracraniană. In: Popescu Irinel(ed), Ciurea AV (ed. Vol. Neurochirurgie), Tratat de Chirurgie, Vol.II, Neurochirurgie, Edit.Academiei Române, 2007.
25. Youmans JR. Neurosurgical Surgery, WB. Saunders Company, 4th ed, 1997.
26. Kay AH. Esential Neurosurgery, second ed, Churchil Livingstone, 1997.
27. Latchaw RE, Kucharczyk J, Moseley ME. Imaging of the Nervous System. Diagnostic and Therapetic Applications, Vol.II, 2005.
28. Lăcrămioara Perju- Dumbravă, Ştefania Kory Calomfirescu, Ioan Florian Ştefan: Neurologie curs pentru studenţi, Ed. Medicală Universitară „Iuliu Haţieganu" Cluj- Napoca, 2002
29. Leira R, Dávalos A, Silva Y, Gil-Peralta A, Tejada J, Garcia M, Castillo J. Stroke Project, Cerebrovascular Diseases Group of the Spanish Neurological Society. Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. Neurology 2004; 63: 461-467.
30. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics-2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. Jan 27, 2009; 119(3): 480-6.
31. Mărginean I, Mureşan D. Patologie neurologică. Vol. 1. Edit. Casa cărţii de ştiinţă. Cluj-Napoca. 1997.
32. Mărginean I. Patologie neurologică. Vol. 2. Edit. Casa cărţii de ştiinţă. Cluj-Napoca. 1997.
33. Pais V, Dănăilă L. Atlas de patologie cerebro-vasculară, Edit.Cartea Universitară, Bucharest, 2005.

34. Popa C. Prevenţia în accidentele vasculare cerebrale. Edit. Medicală Amaltea. Bucureşti. 2000:7-92.
35. Popoviciu L, Aşgian B. Bazele semiologice ale practicii neurologice şi neurochirurgicale, Edit. Medicală, Bucureşti, 1991.
36. Rusu M. Explorarea clinică în neurochirurgie, Edit.Junimea, Iaşi, 1980.
37. Scmideck H.H., Sweet W.H.: Operative Neurosurgical Techniques, Grune and Straton 4th ed, New York, 1997.
38. Sekhar LN, Fessler RG. Atlas of neurosurgical techniques, brain 2006; 523.
39. Sindou M. Curs de Neurochirurgie, Edit. Gh.Asachi, Iaşi, 2001.
40. Singer OC, Sitzer M, du Mesnil de Rochemont R, Neumann-Haefelin T. Practical limitations of acute stroke MRI due to patient-related problems. Neurology 2004; 62: 1848-1849.
41. Szatmari Szabolcs, Szasz Jozsef Atila,Urgente neurologice,2007.
42. Teasdale GM, Jennett B. Assessment of coma and impaired consciousness. Lancet., 1974;ii:1031-4.
43. Teasdale GM, Murray G, Parker L, Jennett WB. ading up the Glasgow coma score. Acta Neurochir (Paris), 1979.
44. Wilkins RH, Rengachary SS. Principles of Neurosurgery, Edit. Wolfe, 1992.

HEMORRHAGIC STROKE

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Contents

1. Definition

The brutal outflow of blood into the brain tissue, caused by a vascular rupture or erythro diapedesis is known by cerebral hemorrhage. The most frequent cause that is incriminated in the apparition of cerebral hemorrhage is arterial blood hypertension.

This form of stroke is the second most common form , but also is the most deadly because unlike the ischemic one, the onset is smooth within minutes to hours and the major symptoms are severe headache, altered level of consciousness and vomiting. The gold standard diagnostic tool in assessing an intracerebral stroke is unenhanced cerebral CT-scan. The size of the hematoma is proportionally with morbidity and mortality and usually the ICH enlargement in most cases is in the first 3 hours of onset.

2. Epidemiology

Cerebral hemorrhage is between 15-30% of the total strokes, being the most common form of stroke. Their frequency of occurrence has increased in the recent years due to the improved diagnostic methods (primarily, the unenhanced cerebral CT scan). The peak incidence on age is between 50-60 years old.

3. Etiology

As written before, arterial blood pressure is the most common cause incriminated in producing this kind of pathology, although is debatable because most of the elder patients already have hypertension but the risk of an intracerebral hemorrhage to occur in a patient with high blood pressure is 4-5 times higher than in a patient without hypertension, so there is a strong correlation between hypertension and intracerebral hemorrhage onset especially at high blood pressure values (above 200 mmHg). In many highly developed countries, in order to prevent the apparition of intracerebral hemorrhage a rigorous treatment of hypertension is initiated and consequently lowering the risk of stroke onset.

Other etiologies incriminated for producing this pathology are atherosclerosis (the hemorrhage produced is because the laceration of a vascular wall), hemopathies and other clotting disorders like leukemia, thrombotic thrombocytopenic purpura, aplastic anemia, patients on treatment like heparin or coumadin, patients receiving thrombolytic therapy, aspirin therapy, vitamin E supplements, CNS infections (fungal, granulomas, herpes simplex encephalitis), venous or dural dural sinus thrombosis, posttraumatic, peripartum and puerperium, drug related substance abuse (alcohol, cocaine, amphetamine) or drugs that raise blood pressure like phenylephrine, ephedrine or ephedra alkaloids and at least but not last, genetic factors present in the form of arterial-venous malformations or cerebral amyloid angiopathy.

The triggering factors of cerebral hemorrhage are: efforts and physical fatigue, positive or negative emotions, states of mental tension, prolonged exposure to the sun, the effort of defecation, sexual intercourse, menstruation, alcohol consumption etc.

4. Pathogeny

In the pathology of intracerebral hemorrhage onset, there are three mechanisms that can cause it:

The first one describes Hemorrhages by arterial vascular rupture, which are usually secondary to hypertension. The production of vascular rupture is conditioned by two factors, that are the conformation of cerebral arterial walls (cerebral arteries have muscular and adventiceal walls thinner than the systemic arteries and do not have external elastic membrane) and the localization of arteries in the basal ganglia and the pontine ones that are ramified directly and perpendicularly to the vessel of origin, so that they transmit high blood pressure in their terminal branches. In large vessels, cerebral hemorrhage is produced as a consequence of the decrease in vascular walls strength through the process of atherosclerosis. In the small arterial vessels, vascular rupture occurs due to the fibrinoid degeneration process of the vascular walls. This process, as well as the accumulation of amyloid in the brain, leads to a decrease of vascular resistance. In congenital malformations (saccular aneurysms like Charcot Bouchard aneurysms, arteriovenous malformations), the existence of some thin wall favours their breaking, usually during an hypertensive episode.

The second mechanism describes hemorrhages by capillary rupture. It is favoured by a sudden increase in the arterial blood pressure in a hypertensive patient. It is preferentially located in a watershed region, corresponding to the boundary between the territories vascularised of two major cerebral arteries, especially at the level of basal ganglia.

And the third mechanism describes hemorrhages by erythrocyte diapedesis. The essential factor of production is encephalomalacia subsequent to an arterial obstruction "hemorrhagic fully transformed infarction". Erythrocyte effusion may be due to a circulatory dysfunction caused by a vascular spasm. The second cause is the return of the arterial blood flow in the capillary bed altered either from the main flow or from the sideline. Their frequency is higher in the basal ganglia and white matter of the different lobes of the brain.

5. Clinical picture

Onset symptoms may be absent but often they precede a few hours from the apparition of the intracerebral hemorrhage. They consist of severe headache, vomiting, dizziness, transient focal symptoms and altered state of consciousness.

There several regions in the brain where a hemorrhage can occur and for that there are several symptoms that can be assessed.

If the hemorrhage is localized in the putaminal region, which is the most common region, the major symptom is a gradual contralateral hemiparesis that can progress to hemiplegia or even coma or exitus.

If the hemorrhage is localized in the thalamic region, classically it will be assessed contralateral hemisensory loss, and if the internal capsule is involved it will appear to have contralateral hemiparesis. If the intra parenchymatous hematoma extends to the upper brainstem then it will appear to have vertical gaze palsy, retraction nystagmus, skew deviation, loss of convergence, palpebral ptosis, anisocoria with or without unreactive pupils.

If the hemorrhage is localized in the cerebellum the symptomatology may include any combination of the following symptoms: lethargy, photophobia, headache, nausea, vomiting, facial palsy if the facial colliculus is compressed due to brainstem compression.

If the hemorrhage is localized in the lobar regions then the symptoms are prominently included in that lobe, like for the frontal lobe- contralateral hemiparesis (in the arm with mild leg and facial weakness) and frontal syndrome, for the parietal lobe - contralateral hemisensory deficit and mild hemiparesis, for the occipital lobe - ipsilateral eye pain and contralateral homonymous hemianopia and for the temporal lobe - on the dominant side, will produce fluent dysphasia with a lack of auditory comprehension and some good repetition.

If the hemorrhage is localized deep into the brain parenchyma and inundating the ventricles then there are some signs that appear, like deep non reactive coma, positive findings at Kernig and Bruzinski signs, rigidity by decerebration with upper limbs in extension and pronation, Babinski sign present bilaterally, early hyperthermia, seizures onset, high effusion of CSF with hemorrhagic spots especially when lumbar

puncture is performed and severe vegetative cardiac and respiratory disorders.

As for the prognosis and evolution, the mortality is at its highest for super acute hemorrhagic stroke and very high for patients being in deep coma or in stuporous state but at 60 + years.

There are some factors that give an unfavorable prognostic to the patient that has intracerebral hemorrhage and they are a concomitant myocardial infarction, decerebrate rigidity, malignant hypertension with elevated arterial blood pressure higher than 250 mmHg and retinal hemorrhages, ventricular flood, cerebro meningeal bleeding, installation of high intracranial pressure syndrome (headache, papilledema, vomiting) with the occurrence of unilateral or bilateral mydriasis and ictus through rigidity decerebration and concomitant presence of gastrointestinal bleeding.

In the diagnosing process of an intracerebral hemorrhage there are some criteria which we should consider that will help a clinician to have a conclusion on the pathology and there are an elevated arterial blood pressure above the 200 mmHg value, sudden onset with rapid entry in deep coma, fast installation of hemiplegia or other focal signs, onset of ictus in full activity, in terms of physical or psychological stress, strong headache followed by vomiting and bloody or hemorrhagic CSF at lumbar puncture.

6. Differential diagnosis

There are several pathologies that differentiate from cerebral hemorrhage and which is good to consider when the patient is assessed.

First of all there is *cerebral ischemia,* against which cerebral hemorrhage is differentiated through the following criteria: **age** (cerebral hemorrhage occurs at younger ages, around 50 years old, cerebral ischemia at younger age); **risk factors** (elevated hypertension, chronic alcoholism pleads for cerebral hemorrhage, while normal blood pressure, coexistence of chronic ischemic heart disease, AF, Chronic Occlusive Arterial Disease of the Extremities, history of transient ischaemic attack all of them suggesting for cerebral ischaemia); clinical signs (sudden onset of headache accompanied by nausea and vomiting, followed by rapid onset of coma advocate for cerebral hemorrhage,

while the slow and progressive installation of a motor deficit directs us to a cerebral ischaemia); cerebral hemorrhage occurs more frequently during the day, while cerebral ischaemia at night; vegetative disorders and fever are more common in cerebral hemorrhage; anisocoria and unilateral mydriasis occur more often in cerebral hemorrhage; the presence of meningeal and ventricular flood signs are incriminating in cerebral hemorrhage and the presence of retinal hemorrhages at the ophthalmologic exam calls for a cerebral hemorrhage.

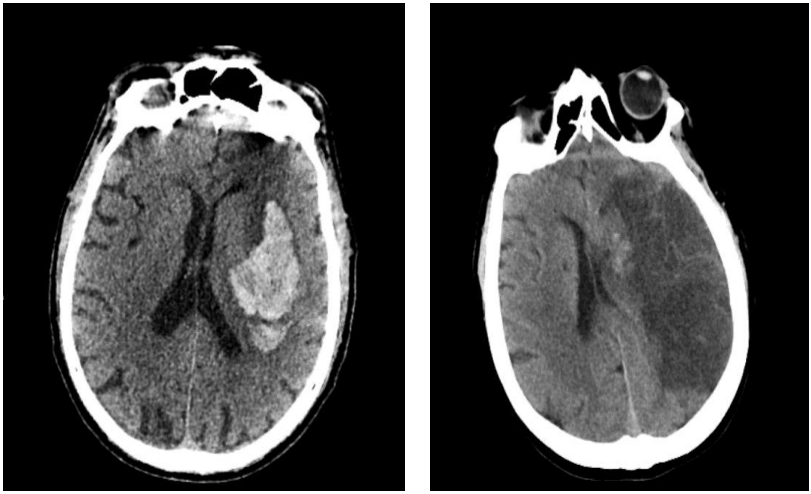

Figure ***1.*** *In the left aspect there is an image showing a cerebral CT-scan of an intra parenchymatous hematoma in contrast with the right aspect where it shows an ischaemic stroke.*
(Personal collection of dr. Vicențiu Săceleanu)

Second pathology is the subarachnoid hemorrhage that occurs in the normotensive young people with intracranial vascular malformations. Focal signs are less expressed as in cerebral hemorrhage. Laboratory examinations (angiography, brain CT scan) complete the diagnosis.

In the third case, hypertensive encephalopathy occurs in the patients with chronic hypertension in whom an ICP syndrome is rapidly installed. Cranial CT scan does not show typical signs of cerebral

hemorrhage. Lumbar puncture (pay attention to ICP syndrome!) reveals a clear CSF, slightly hypertensive.

On the fourth hand, subdural and extradural hematoma for whose diagnosis, history matters (history of TBI), more rapid installation of the clinical symptoms, cranial CT scan.

On the fifth point there are extensive intracranial processes in which the specific symptoms are focal signs that occur regionally dependent, and the evolution slower, progressive. The lesion on the enhanced CT-scan is characteristic. As for brain abscesses, usually the infectious syndrome is incriminated together with focal signs and the specific cranial CT.

The last pathological entity is the postcritical epileptic coma in which anamnesis is of great importance. Clinical signs reversibility is characteristic (especially after the specific treatment administration). Cranial CT scan is normal and the EEG is characteristic.

7. Paraclinical investigations

The most representative paraclinical investigations are the lumbar punctures that reveal a hemorrhagic CSF (it should be performed after the ophthalmologic exam, because of the risk of high intracranial pressure syndrome). The presence of cerebral hemorrhage is found when the smear shows more than 50 red blood cells per mmc.

The eye examination may reveal retinal hemorrhages or papilledema, if the intracranial pressure is high.

In a comatose it is contraindicated to perform an arteriography. On the other hand in a normal state set up, this investigation can give information about the existence of an aneurysm, AVM or about an intracranial expansive process.

The gold standard investigation in assessing a cerebral hemorrhage is the unenhanced cranial CT scan, which establishes the location and the extent of the injury with the blood entering the subarachnoid space or the ventricular system. Hematoma volume calculation is done by the ellipsoid formula, measured on the computer image, where A is the largest diameter of the hematoma, B is the maximum anterior-posterior diameter and C is the number of images at 1 cm, on which the hematoma appears.

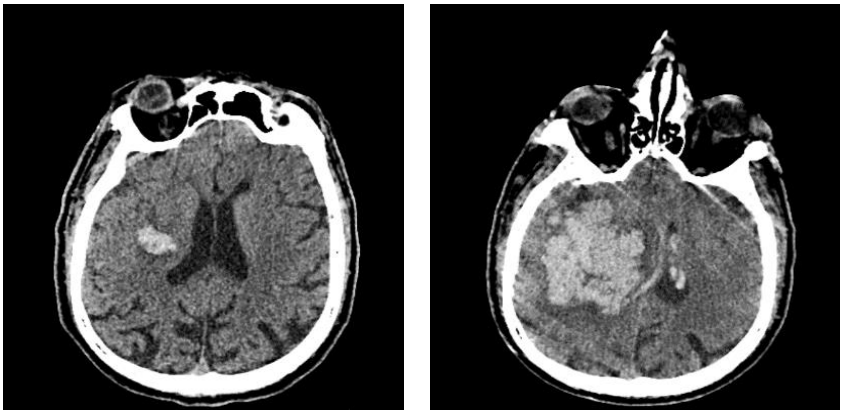

*Figure **2.** Two cerebral CT-scans showing a small intraparenchymal hematoma (left) and after 7 hours a gigantic hematoma at the same patient (right). (Personal collection of dr. Vicențiu Săceleanu).*

The MRI examination is a noninvasive method which shows foci of lower size petechial hemorrhages than those observed by cranial CT scan.

At last but not least is angio-CT scan that is now used in case of suspicion of a ruptured aneurysm, an AVM, abnormal calcifications, blood present in the interhemispheric fissure, Sylvian valley or isolated bleeding in cerebral ventricles. The value of cerebral angio-CT is inversely proportional with the age of the patient especially for those who are over 45 years old and who have a history of hypertension, or putaminal, thalamic or posterior fossa hemorrhage. This investigation can assess the presence of moyamoya, cerebral venous thrombosis, brain tumors or arteriovenous malformations.

8. Treatment

8.1. Medical treatment

Before surgery is performed or before thinking of surgery in the case of a patient with a intracerebral hemorrhage, first the respiratory function must be monitored (oxygen intake, bronchial secretions aspiration, controlling the partial pressure of the carbon dioxide and maintaining it at 25-30 mmHg) and the cardiovascular system by

lowering the arterial blood pressure with anti hypertensive medication like beta-blockers and angiotensin-converting-enzyme inhibitors and the treatment of heart rhythm disorders and cardiac ischaemia. Attention at calcium channel blockers because they have a higher risk to produce intracranial pressure.

Another aspect in the prodromal treatment is treating the cerebral edema with mannitol, diuretics and glycerol. Controlling the use of cell dehydrators, such as mannitol with an osmolarity that should be preserved between 295-305 mosmol/l and between 145-150 mEq natrium. The electrolyte and acid-base disorders should be treated intravenously or by nasogastric tube limiting the administration of fluids to 1200 ml/day intravenously under the form of saline perfusion.

As for the adjuvant treatment there can be used hemostatic treatment (epsilon-aminocaproic acid, adrenostazin or venosta), neuroprotectors like nimodipine or piracetam intravenously, treatment of psychomotor agitation and seizures like phenobarbital intramuscular or diazepam slowly intravenous, because it can suppress the breathing centers, vomiting treatment with metoclopramide or osetron intravenously, hyperthermia treatment by administering paracetamol intravenously and if necessary antibiotics and treatment of sphincter disorders of urine retention type.

The patient rehabilitation after cerebral hemorrhage consists of a set of methods aimed to maintain and restore patients to a satisfactory physical and neuropsychological status, followed by the motor recovery whose goal is family and, if possible, the socio-professional reinsertion. As a first step, a patient's position in bed will be changed periodically at an interval of 2 hours for the prevention of bedsores. Later, one can proceed to massage (to preserve muscle tone and prevention of pressure sores), passive and active kinesiotherapy and finally, physiotherapy treatment.

8.2. Surgical treatment

In a neurosurgery practice, there are known four procedures that can drain an intraparenchymal hematoma by simple aspiration; by performing a craniotomy or a craniectomy (open surgery); by endoscopic approach or by stereotactic approach.

The main objectives in a surgical approach to the intraparenchymal hematoma are by importance reducing the blood volume of the hematoma, reducing the mass effect of the hemorrhagic collection, increasing the blood perfusion to the damaged hemisphere, seize the opportunity in stopping the bleeding and eliminating the thrombin and blood degradation products consequently reducing the chance in forming a neurotoxic edema.

There are several clinical criteria that plead for performing a surgical intervention and those are as soon as possible from the onset surgery, CT-scan observation of a intraparenchymal blood collection that can endanger patient's life (usually assessing by the GCS deterioration), the instalment of any of these symptoms: hemiparesis, hemiplegia, aphasia, confusion (although signs of increased intracranial pressure), drug treatment failure evidentiated by intracranial pressure increase and the age of a patient higher than 50 years.

Beside the clinical criteria, a clinician must take in consideration the imagistic criteria that can advocate for a surgical intervention and they are according to the calculated volume between 10-30 cubic centimeters and midline shift greater than 5 mm. An intraparenchymal hematoma volume higher than 30 cubic centimeters is associated with reserved prognosis.

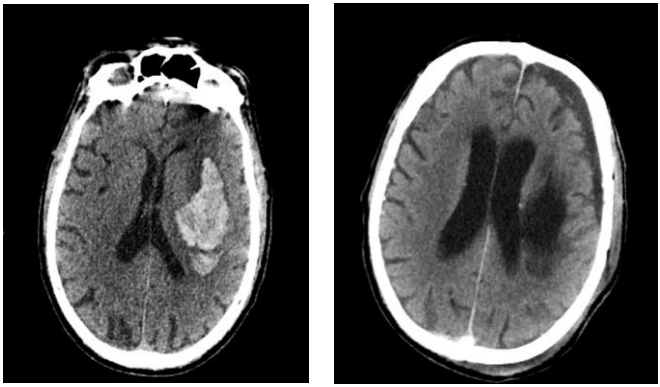

*Figure **3.** These images are two cerebral CT scans that show an intra parenchymal hematoma before surgery (left) and after surgery (right). (Personal collection of dr. Vicențiu Săceleanu).*

For a conservative treatment procedure there are some clinical criteria and there are: a good neurological status with a GCS higher than 10, low motor deficit, a good therapeutic response to cerebral depletion treatment, severe bleeding disorders or organic diseases in which the neurological status can rapidly worsen, patients with an age higher than 74 years who do not tolerate a surgical intervention and intraparenchymal treatment at the basal nuclei level in which case can have a better outcome with conservative treatment.

For those cases that have poor prognosis, in which a potential benefit of an intervention is null there are some criteria that should be considered: severe coma, installation of major respiratory disorders, significant hemorrhage with massive destructions and major bleeding in the dominant hemisphere.

There are some cases in which the surgical treatment is not recommended and there is a hematoma volume greater than 85 ml with no survival chances, excessive bleeding with bilateral extension and midline structures shifted contralaterally and massive hemorrhage with brain stem seriously damaged.

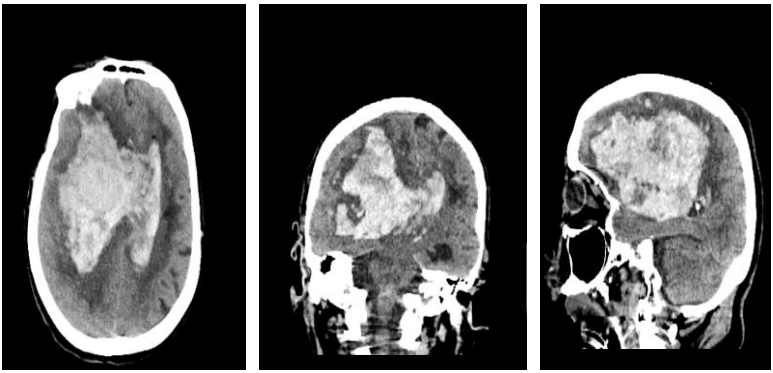

*Figure **4.** These images show a cerebral CT scan performed for a comatose patient (GCS=3 pct) with mydriatic non reactive pupils with a gigantic intra parenchymal supratentorial hematoma - transversal aspect (left), coronal (center), sagittal (right).*
(Personal collection of dr. Vicențiu Săceleanu).

Disclaimer: *The authors have no conflicts of interest to declare.*

References:

1. Adam D. Compendiu de neurotraumatologie, Editura didactică şi pedagogică, Bucureşti. 2009.
2. Arseni C. Boli vasculare ale creierului, vol 2, partea a II-a, Ed. Academiei Române, Bucureşti, 1984.
3. Arseni C. Tratat de Neurologie, Edit. Medicală, 1982.
4. Arseni C, Popoviciu L. Semiologie neurologică, Edit.Didactică şi Pedagogică, Bucureşti, 1983.
5. Băjenaru O. Ghid de diagnostic si tratement în neurologie, 2010.
6. Borstein NM, Chemmanam T, Davis S. Stroke, Basel, Karger, 2009; 174-175.
7. Butcher KS, Baird T, Parsons MW, Davis S. Medical management of intracerebral hemorrhage, Neurosurg.Q, 2002; 12: 261-278.
8. Ciurea AV, Constantinovici A. Ghid practic de Neurochirurgie, Edit.Medicală, 1988.
9. Ciurea AV. Patologia neurochirurgicală. Tratat de patologie chirurgicală, sub red.N. Angelescu, Vol. II, Edit. Medicală, Craiova, 2001.
10. Ciurea AV, Iacob G. Tehnici neurochirurgicale, Edit. Cartea Universitară, Bucureşti, 2006.
11. Ciurea AV. Tratat de Neurochirurgie, vol. 1, Edit. Medicală, Bucureşti, 2010.
12. Ciurea AV. Tratat de Neurochirurgie, vol.2, Edit. Medicală, Bucureşti, 2011.
13. Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk AM, Hill MD, Patronas N, Latour L, Warach S. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet 2007; 369: 293-298.
14. Florian I St. Neurochirurgie. Curs pentru studenţi, Cluj-Napoca, Edit.Srima, 2003.
15. Florian I St, Perju-Dumbravă L. Opţiuni terapeutice în accidentele vasculare hemoragice, Edit. Medicală Universitară, Iuliu Haţieganu, Cluj-Napoca, 2007; 12-26, 67-73.
16. Fung C, Murek M, Z'Graggen WJ, Krähenbühl AK, Gautschi OP, Schucht P, et al. Decompressive hemicraniectomy in patients with supratentorial intracerebral hemorrhage. Stroke 43:3207–3211, 2012.
17. Gebel JM Jr, Jauch EC, Brott TG, Khoury J, Sauerbeck L, Salisbury S, et al. Natural history of perihematomal edema in patients with hyperacute spontaneous intracerebral hemorrhage. Stroke 33:2631–2635, 2002.

18. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a guideline for health care professionals from the American Heart Association/American Stroke Association. *Stroke.* Feb 2011; 42(2): 517-84.
19. Goldste**in** LB, Simel DL**.** Is this patient having a stroke? JAMA 2005; 293: 2391-2402.
20. Gorgan RM. Ghid în patologia neurochirurgicală, Editura didactică și pedagogică, București, 2008.
21. Greenberg MS. Handbook of Neurosurgery, Thieme, Medical Publishers, New York, 2020.
22. Hachinsky VC. Advances in Stroke 2002: introduction, Stroke, 2003, 34:323.
23. Ienceanu StM. Actual state in intracranial hipertension, Edit. Gh.Asachi, Iași, 2003.
24. Ienceanu ȘtM, Ciurea AV. Hipertensiunea intracraniană. In: Popescu Irinel(ed), Ciurea AV (ed. Vol. Neurochirurgie), Tratat de Chirurgie, Vol.II, Neurochirurgie, Edit.Academiei Române, 2007.
25. Youmans JR. Neurosurgical Surgery, WB. Saunders Company, 4th ed, 1997.
26. Kanno T, Sano H, Sh**in**omiya Y, Katada K, Nagata J, Hoshino M, Mitsuyama F. Role of surgery in hypertensive intracerebral hematoma: a comparative study of 305 nonsurgical and 154 surgical cases. J Neurosurg. 1984; 61: 1091-1099.
27. Kay AH. Esential Neurosurgery, second ed, Churchil Livingstone, 1997.
28. Kidwell CS, Chalela JA, Saver JL, et al. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. Jama 2004; 292: 1823-1830.
29. Latchaw RE, Kucharczyk J, Moseley ME. Imaging of the Nervous System. Diagnostic and Therapetic Applications, Vol.II, 2005.
30. Lăcrămioara Perju- Dumbravă, Ştefania Kory Calomfirescu, Ioan Florian Ştefan: Neurologie curs pentru studenţi, Ed. Medicală Universitară „Iuliu Haţieganu" Cluj- Napoca, 2002
31. Leira R, Dávalos A, Silva Y, Gil-Peralta A, Tejada J, Garcia M, Castillo J**. Stroke** Project, Cerebrovascular Diseases Group of the Spanish Neurological Society. Early neurologic deterioration **in in**tracerebral hemorrhage: predictors and associated factors. Neurology 2004; 63: 461-467.
32. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics-2009 update: a report from the American Heart Association Statistics Committee and

Stroke Statistics Subcommittee. *Circulation.* Jan 27, 2009; 119(3): 480-6.
33. Mayer SA, Rincon F. Treatment of intracerebral haemorrhage, Lancet Neurol 2005; 4: 662-672.
34. Mărginean I, Mureşan D. Patologie neurologică. Vol. 1. Edit. Casa cărţii de ştiinţă. Cluj-Napoca. 1997.
35. Mărginean I. Patologie neurologică. Vol. 2. Edit. Casa cărţii de ştiinţă. Cluj-Napoca. 1997.
36. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet.* Jan 29-Feb 4 2005; 365(9457): 387-97.
37. Morgenstern LB, Hemphill JC 3rd, Anderson C, Becker K, Broderick JP, Connolly ES Jr, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* Sep 2010; 41(9): 2108-29.
38. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneus intracerebral hemorrhage, N. Engl. J. Med. 2001, 344, 1450-1460.
39. Pais V, Dănăilă L. Atlas de patologie cerebro-vasculară, Edit.Cartea Universitară, Bucharest, 2005.
40. Popa C. Prevenţia în accidentele vasculare cerebrale. Edit. Medicală Amaltea. Bucureşti. 2000:7-92.
41. Popoviciu L, Aşgian B. Bazele semiologice ale practicii neurologice şi neurochirurgicale, Edit. Medicală, Bucureşti, 1991.
42. Sacco RL. Lobar intracerebral hemorrhage, NEJM 2000; 342(4): 276-279.
43. Săceleanu V. Opţiuni terapeutice şi strategii de reinserţie socială în hemoragia intracerebrală primară supratentorială, Teză doctorat, Sibiu, 2011.
44. Scmideck H.H., Sweet W.H.: Operative Neurosurgical Techniques, Grune and Straton 4th ed, New York, 1997.
45. Sekhar LN, Fessler RG. Atlas of neurosurgical techniques, brain 2006; 523.
46. Sindou M. Curs de Neurochirurgie, Edit. Gh.Asachi, Iaşi, 2001.

47. Singer OC, Sitzer M, du Mesnil de Rochemont R, Neumann-Haefelin T. Practical limitations of acute stroke MRI due to patient-related problems. Neurology 2004; 62: 1848-1849.
48. Steiner T, Kaste M, Forsting M, et al. Reccomandation for the management of intacranial haemorrhage. Spontaneus intracerebral haemorrhage. The European Stroke Initiative Writing Committe and the Writing Committee for the EUSI Executive Committee. Cerebrovasc Dis. 2006; 22: 294-316.
49. Szatmari Szabolcs, Szasz Jozsef Atila,Urgente neurologice,2007.
50. Teasdale GM, Jennett B. Assessment of coma and impaired consciousness. Lancet., 1974;ii:1031-4.
51. Teasdale GM, Murray G, Parker L, Jennett WB. ading up the Glasgow coma score. Acta Neurochir (Paris), 1979.
52. Wilkins RH, Rengachary SS. Principles of Neurosurgery, Edit. Wolfe, 1992.

SUBARACHNOID HEMORRHAGE

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Non est vivere, sed valere, vita
Marțial, Epigrame, (VI, 60)

Contents

1. Introduction. Anatomy basics

The cerebrospinal fluid fills up the cerebral ventricles and the subarachnoid space.

The subarachnoid space in the encephalus has dilations named cisterns which are crossed mainly by critical vessels of the cerebral circulation.

The lateral cerebral ventricles are connected to the third ventricle through the foramina of Monroe, the third ventricles is continued by the sylvian aqueduct which connects it to the fourth ventricle.

The fourth ventricle is connected to the subarachnoid space through the foramina of Lushka (cerebello-pontine angle cistern) and though the foramen of Magendie (cisterna magna or the cerebello-medullary cistern) and is continued in the spinal cord by the ependymal canal.

Subarachnoid hemorrhage occurs as a consequence of a blood vessel rupture in the subarachnoid space or near it. Following this rupture, blood will invade the space between the pia mater and the arachnoid, the subarachnoid space, which normally contains just cerebrospinal fluid.

2. Epidemiology

Etiologically, which is considering the reason that led to the event, following types of SAH stand out – traumatic SAH or spontaneous. The spontaneous form of SAH occurs in cases of high arterial blood pressure (hypertensive SAH) or is the direct consequence of an aneurysmal rupture, a cerebral or spinal arterial-venous malformation rupture or secondary to cervical-cerebral arteries dissection. ***Actually about 85% of all SAH forms are due to the rupture of a cerebral aneurysm. Brain aneurysm typically occurs during spring and autumn and is considered directly linked to temperature changes, similar to CVAs.*** *(2,4,6)*

A rare form of spontaneous SAH is the idiopathic subarachnoid hemorrhage, in the presence of ***risk factors considered non-traditional and modifiable*** – alcoholism, smoking, cocaine or amphetamine abuse. Besides these forms, literature provides a series of ***traditional risk factors,*** which are ***not subject to medical or lifestyle intervention*** and thus called *non-modifiable*, frequently linked to SAH occurrence: family history of SAH, soft tissue disease (polycystic kidney disease, neurofibromatosis type I, Ehlers-Danlos syndrome mainly type IV and other collagen abnormalities), female sex (1.5 times the risk), African descent (2 times the risk), Japanese or Finnish descent, vasculitis, even more rare factors – parasitosis, Moya-Moya disease, eclampsia, blood disorders, coagulation disorders. *It is important to point out that as*

prevalence of the non-modifiable risk factors gets higher, it is expected that SAH incidence will increase in the following decades. (2,4,5,6,7)

About a quarter of all subarachnoid hemorrhages in children and adolescents, spontaneous and traumatic as well, happen in the presence of a cerebral tumor.

When it comes to intracranial aneurysms in the pediatric age group a particular aspect stands out, being noticed that a dominance of 2.2:1 of boys versus girls exists, as opposed to female aneurysms occurrence versus men in the adult population. (3)

When it comes to the site of aneurysms in children and adolescents the frequency varies with the number of aneurysms found in a single individual. For a ***single aneurysm,*** the most predisposed sites are the internal carotid artery bifurcation, the ophthalmic artery, the anterior communicating artery, the posterior communicating artery, the anterior cerebral artery, the pericallosal artery, and then the middle cerebral artery. ***Multiple aneurysms*** are found, sorted by the highest frequency, on the middle cerebral artery, anterior communicating artery and internal carotid artery bifurcation. (1,3)

A particular subset consists of ***mycotic aneurysms,*** which are indeed a large subset of aneurysms (4%) among pediatric patients when compared to adults. Casual causes of these mycotic aneurysms are bacteria and not fungus, which is why some authors are more comfortable with the term of *infectious aneurysms. Among the most incriminated bacterial agents are Staphylococcus* Aureus, alpha-hemolytic streptococcus and Hemophilus in immunocompetent patients and Aspergillus, Candida and Phycomycetes in immunocompromised patients. (2,3)

Infectious aneurysm in children are secondary to septic emboli from severe bacterial infections, most commonly bacterial endocarditis. Other types of aneurysmal septic embolic syndrome include dissemination from close situs like meningitis, sinusitis or osteomyelitis.

3. Clinic of subarachnoid hemorrhage

The first symptom or the ***princeps*** and nonetheless the most constant (about 97% percent of cases) is severe headache with

- sudden onset – described in the Anglo-Saxon literature as a *thunderclap headache* and

- acknowledged by the patient as "the most intense headache I ever had".

A more particular situation is the ***sentinel headache*** – a sudden and severe pain that goes away, allowing for a symptom-free period with neglection of said episode, followed shortly by severe mental status alteration, paroxysmal phenomena known by neurosurgeons as ***"walk, talk and die patients."*** (6)

Photophobia as an accompanying symptom is frequent, together with ***ocular symptoms*** such as subhialoid hemorrhage, retinal or vitreous hemorrhage.

Eye fundus examination may reveal papillary edema secondary to increased intracranial hypertension, secondary to bleeding into the subarachnoid space. In medical literature vitreous hemorrhage associated with SAH is known as Terson's syndrome.

Vegetative phenomena such as ***emesis or syncope*** are common. Sometimes and not rarely, the patient seeks medical attention after a loss of consciousness or in altered mental status. The neurological and mental status varies greatly even on debut from slight confusion or drowsiness to deep coma.

Epileptic seizures occur frequently as about 20% of patients develop such symptoms in the first 24 hours since debut. They are considered to be a straight effect of cortical irritation by the blood effused in the subarachnoid space and equally due to increased intracranial pressure, associated hyponatremia or aneurysm stent (especially when it involves sylvian arteries territory).

Neurological examination reveals following symptoms and signs:

- ***meningeal signs, with early debut: neck stiffness, headache, photophobia, ocular pain, emesis.*** Neck stiffness usually develops within 6 to 24 h from the debut of SAH. Within a few hours from debut signs such as Kernig, Brudzinki or bilateral Lassegue can appear
- ***altered neurological status*** – varies on patient admission from fully conscious to drowsiness and disorientation both in time and space or when it comes to the self, obnubilation or even coma
- ***focal neurological signs*** – they point to the situs of the lesion

- **accompanying signs or symptoms** are acute urinary retention, diminished or abolished osteo-tendinous reflexes (usually after 4 to 6 h from the debut of the hemorrhage)
- ***psychiatric acute onset*** - the elderly are more likely to be in a far worse neurological status on debut and to develop psychiatric symptoms similar to dementia or worsened dementia.

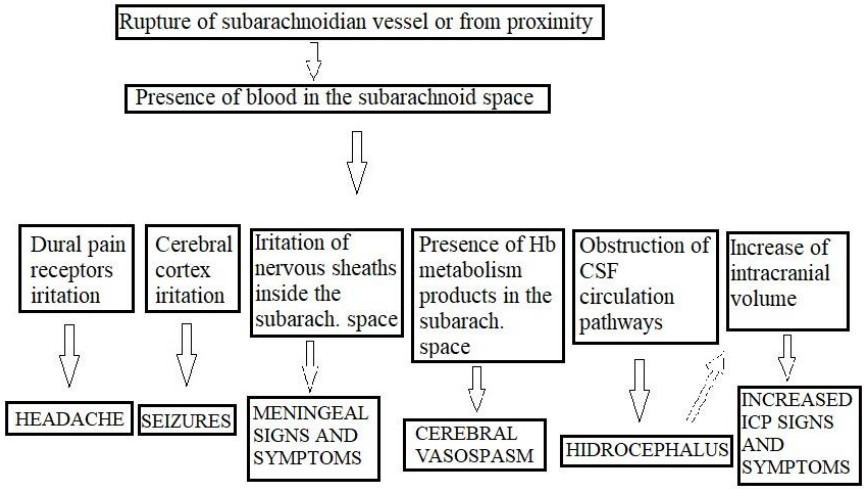

Figure 1. Illustration regarding the pathological mechanisms of SAH complications – personal illustration

The neurological status of the patient suffering from SAH is to be appreciated with the help of ***Hunt & Hess scale (1968) and WNFS scale (World Neurosurgical Federation Society scale, 1988)*** and it is extremely important in the surgical indication. (7,11) Classification into a Hunt & Hess grade is determined after clinical and neurological assessment as follows:

H&H Grade	
I	mild or moderate headache, absent or mild neck stiffness
II	severe headache, neck stiffness, cranial nerves palsy
III	confusion or lethargy, mild focal deficit
IV	stuporous, moderate or advanced hemiparesis, decerebrate
V	comatose, decerebrate

Figure 2. Hunt & Hess Scale

WFNS Scale (1988) is based upon Glasgow score (GCS, Glasgow Comma Scale) and the presence or absence of neurological deficits as such:

WFNS grade	
I	GCS=15, no neurological deficits
II	GCS=13-14, no neurological deficits
III	GCS=13-14, neurological deficits
IV	GCS=7-12, whatever the neurological deficits
V	GCS=3-6, whatever the neurological deficits

Figure 3. WFNS grades

4. Diagnosis of subarachnoid hemorrhage

The elective diagnostic tool in SAH is the ***plain cerebral CT examination*** on arrival in the emergency room, which shows blood in the subarachnoid space. ***The Fisher grade (1980)*** is thus immediately established. This diagnostic imaging tool is nonetheless the actual ***gold standard*** in diagnosing the subarachnoid hemorrhage, its limitation

being that when not enough time since the debut of the hemorrhage has passed, the first examination might turn out negative and will become positive a few tens of minutes later. (7) The Fisher grading system is based upon the results of the plain cerebral CT examination and it appreciates the risk of developing cerebral vasospasm. It is summarized in the table below. (10)

Fischer grade	Presence of subarachnoid blood	Others features	Vasospasm risk
Grade 1	No cisternal blood	No clots	21%
Grade 2	Blood < 1mm thickness	No clots	25%
Grade 3	Blood > 1mm thickness	With or without clots	37%
Grade 4	Small amount of blood, diffuse and in the basal cisterns	Parenchymal or intraventricular hemorrhage	21-37%

Figure 4. Fisher scale

If the CT examination is negative but the clinical suspicion of SAH is still high, a lumbar puncture may be helpful for diagnostic purpose, but it is to be performed with every precaution and only after eye fundus examination excludes intracranial hypertension, in order to avoid cerebral herniation. (5,7)

Lumbar puncture is according to available date the most sensitive diagnostic tool for SAH. A positive result consists of increased CSF pressure, ***xanthochromic CSF, more than 100 000 thousand erythrocytes per mm3, increased proteinorrhachia (>50 mg/dl) and normal or slightly decreased glycorrhachia (<50-70 mg/dl).***

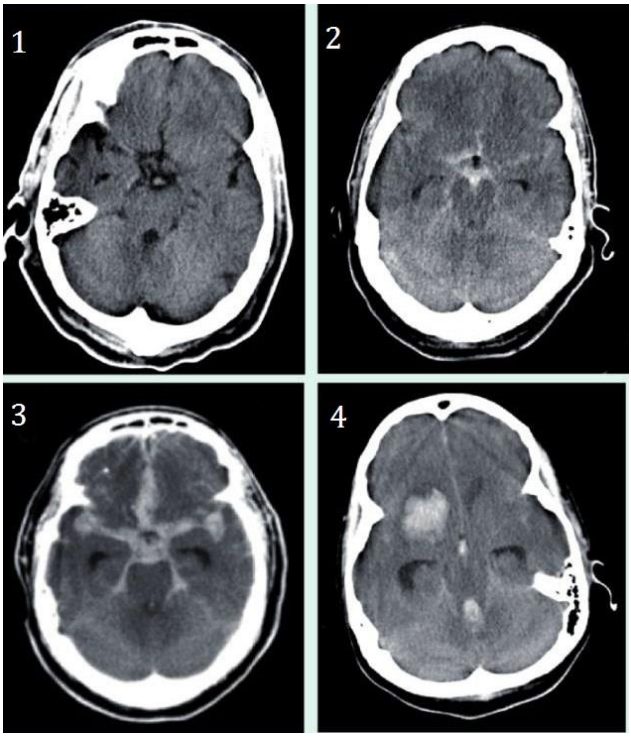

Figure 5. Cranio-cerebral CT axial sequences showing the 4 Fisher grades (1 – grade 1, 2 – grade 2, 3 – grade 3, 4 – grade 4).
(Image source: Future Neurol @ 2013 Future Medicine Ltd)

Cerebral MRI imaging with FLAIR sequencing, CT angiography or MRI angiography do not add very much relevance to the SAH diagnosis in the first 24-48 hours following debut, but they prove to be excellent between day 3 and 7, with good premises for identifying a cerebral aneurysm and its anatomical features.

Digital subtraction angiography (DSA) – consists of selectively injecting contrast material using a catheter inserted into a large artery under radiologic screen. It is an extremely useful resource in the evaluation of cerebral aneurysms and it can also come in as a both diagnostic and therapeutic tool, providing the possibility of simultaneously embolizing the incriminated aneurysm or AVM.

Aneurysm with sacs smaller than 5 mm are ideal for endovascular coiling, while for the rest of them the risk of recanalization or incomplete occlusion are considered too high, thus needing stent or balloon assisted coiling. (5,7,9)

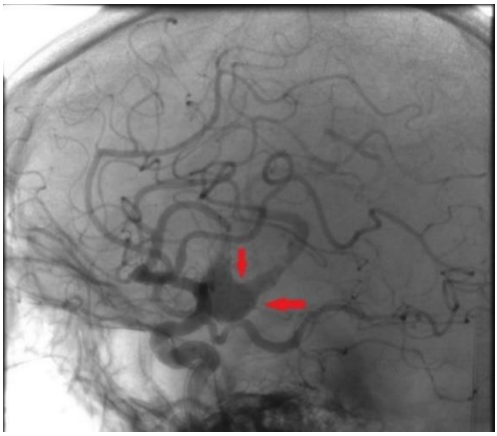

Figure 6. DSA frame – large dissecting aneurysm of the right sylvian artery - M2 segment
(Image source: Neurosurgery I clinic collection, Emergency University Hospital of Bucharest)

5. Management and complications

The right moment to perform surgery in aneurysmal SAH is nowadays considered to be at 24-72 hours from debut in patients with Hunt & Hess grades 1 or 2 and consists of aneurysm securement through classical surgical clipping or endovascular coiling. Patients with a higher Hunt & Hess grade are to be admitted and monitored in the intensive care unit for vital functions support with the goal of obtaining a better neurological status in order for the aneurysm securement to be achievable with a more favorable risk/benefit balance. (3,4,5)

Exception to this rule occurs when SAH of any etiology is accompanied by large parenchymal hematoma (Fisher grade IV) that come with vital risk to the patient and it requires ***emergency intervention*** whatever the Hunt & Hess grade. A similar situation occurs when

patient's life is endangered on the sort-term due to intracranial hypertension (secondary to acute obstructive hydrocephalus following SAH) - a external ventricular drainage is placed together with an *intracranial pressure monitoring device* – in order to obtain clinical and neurological amelioration until definitive treatment of the cause that led to SAH is possible. (3,4,5,7)

Following surgery, after securing the aneurysm whose rupture produced the subarachnoid hemorrhage, together with general medical measures and complications prevention, a transcranial Doppler ultrasound is needed in order to appreciate the blood flow through the main cerebral arteries and possible vasospasm, as well as control cerebral CT examination for the verifying of occlusion devices used and for the visualizing the aspect of the ongoing SAH. In cases of drug resistant vasospasm *intraarterial endovascular vasodilator therapy* may be used – vasodilator agents are selectively injected directly into the cerebral arteries under angiographical control. (7,8,9)

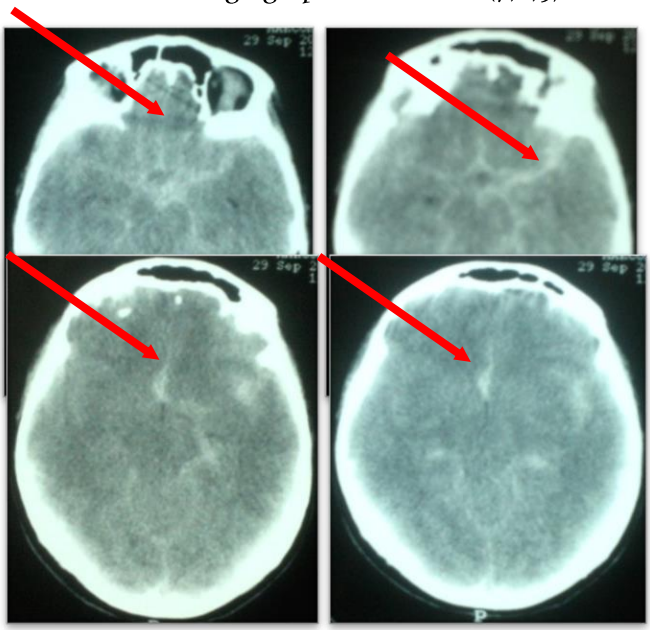

Figure 7. CT-scan: preoperatory vasospasm of ACA. Patient is pharmacologically managed with nimodipine (calcium channel blocker)

(Personal case Prof. Dr. AV Ciurea)

6. Expectations and neurological rehabilitation

In the postoperative period medical treatment measures must be continued. Considering the risk of rebleed, which stand at 30-70% despite adequate treatment and knowing that 90% of rebleed lead to death, postsurgical patients must be monitored in the intensive care unit.

Despite these therapeutic resources, the major risk of devastating complications particularly difficult to treat persists – cerebral vasospasm and late cerebral ischemia, vegetative phenomena of central origin, parenchymal hematoma, rebleed, electrolytes imbalance, normal pressure hydrocephalus. (4,5)

The risk of developing cerebral vasospasm stands present since the debut of SAH but is considered to be at its highest between days 3-7 and extending up to 3 weeks. It is very accurately appreciated with the help of the Fisher grading system, risk correlation being proportionate with a higher grade. (8,9,11)

A *curative treatment* of subarachnoid hemorrhage is out of the question at the moment, with it being not actually a disease but rather a course of pathological events that develop in a chain like manner and that imply a series of serious consequences over cerebral structures, both short term and long term.

Abreviations: **ACA** – Anterior Cerebral Artery; **CT** – computerized tomography*;* **CSF** – cerebro-spinal fluid; **ICP** – increased intracranial pressure*;* **MRI** – magnetic resonance imaging*;* **SAH** – subarachnoid hemorrhage

Disclaimer: The authors have no conflicts of interest to declare.

References:

1. Bibirita A, Teleanu D, Mohan A, Ciurea A.V., Hemoragia Subarahnoidiană la Copil și Adolescent, Revista de Neurologie si Psihiatrie a Copilului si Adolescentului din Romania, vol 26, nr 4, dec 2020
2. Ciurea A.V., Tratat de neurochirurgie, editura Medicala, 2011, vol 2, pag 81-96

3. Constatinovici A, Ciurea A.V., Ghid practic de neurochirurgie, editura Medicala, 1998, pag 351-368
4. Danaila L, Stefanescu F, Anevrismele cerebrale, ed.Academiei Romane, Bucuresti, 2007, pag. 44-63
5. Ellenbogen R, Laligam S, Florian I.S., Principiile chirurgiei neurologice, ed 4, Editura Hipocrate, 2019, cap 16:254-263, 23:343-354, 24:355-365
6. Gorgan M, Neurochirurgie – note de curs, ed 2, cap 3:85-106
7. Greenberg M.S., Handbook of Neurosurgery, 8th editia a 8a, 77:1156 - 1171
8. Schmideck & Sweet Operative: Neurosurgical Techniques, 6th edition, Elsevier, 2012, 84:1019-1028, 93:1115-1125
9. Youmans and Winn Neurological Surgery, editia 7, Elsevier, 2017, 379:3232-3256, 380:3257-3273
10. Lindvall P, Runnerstam M, Birgander R, Koskinen LO. The Fisher grading correlated to outcome in patients with subarachnoid haemorrhage. Br J Neurosurg. 2009 Apr;23(2):188-92.
11. Rosen DS, Macdonald RL. Subarachnoid hemorrhage grading scales: a systematic review. Neurocrit Care. 2005;2(2):110-8.

INTRACRANIAL ANEURYSMS

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"Discovery means seeing what everyone sees and thinking about something that no one else has ever thought of"
Albert von Szent – Gyorgy (1893 – 1986)

Contents

1. General Data

Intracranial aneurysms (IA) represent a localized enlargement of a blood vessel (more frequently arteries than veins) caused by a cerebrovascular disorder in which the vessels' walls are weak. IA have high morbidity and mortality while subarachnoid hemorrhage (SAH) due to IA rupture is responsible for most clinical symptoms. In a significant number of cases, IA rupture is associated with one or more of the following forms of hemorrhage: intraparenchymal hematoma, intraventricular hemorrhage, subdural hematoma. Virtually any subarachnoid hemorrhage should be investigated and treated from the outset with the suspicion of aneurysmal rupture - unless the clinical context points to another diagnosis. The main cause of morbidity and mortality is the repetition of aneurysmal rupture in cases where the aneurysm is not treated (surgically or endovascular).

IA can be classified by size, shape or vessel wall:

A. Size
   - Small IA - diameter < 15mm
     - Micro IA (Charcot Bouchard aneurysms) are usually located in blood vessels with a diameter smaller than 300 microns, usually concerning lenticulo-striate vessels of the basal ganglia. They are associated with systemic arterial hypertension.
   - Large IA - diameter > 15mm
     - Large - diameter = 15 to 25 mm
     - Giant - diameter = 25 to 50 mm
     - Super giant - diameter > 50 mm

B. Shape
   - Saccular IA
     - Because of the shape, they are often called "berry aneurysms" - round vessel enlargement. They are also the most common IA.

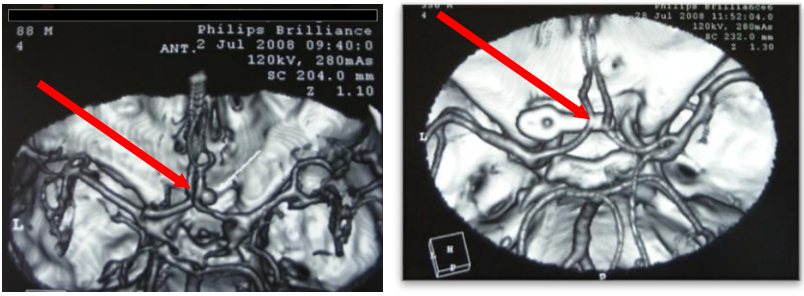

Figure 1. Anterior communicating artery aneurysm (saccular) in an 88-year patient and postoperatory angiography view of the clipped aneurysm (Personal collection of Professor AV Ciurea and Assistant Professor AG Mohan)

- Fusiform IA
  - This type of IA represents both an elongation and distension of the entire vessel, often resulting from dissections when blood ruptures in the wall of an artery. They are referred to as dolichoectatic IA and have a smaller chance of rupture. They are most frequently found at vertebral and basilar artery.

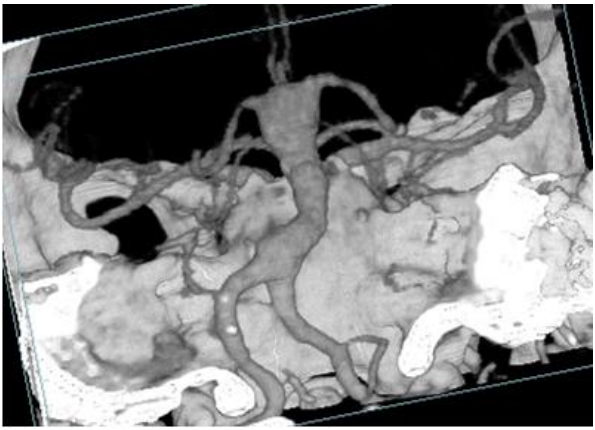

Figure 2. Aneurysm of the basilar artery (fusiform). (Personal collection of Professor AV Ciurea)

C. Vessel wall

- True aneurysms - in this category are included the IA that involves all three layers of an artery - intima, media and adventitia.
- False aneurysms (pseudoaneurysms) - a collection of blood accumulated outside the vessel but still in contact with its outer layer due to the surrounding connective tissue which prevents blood from spreading out. Usually, they evolve with either thrombosis or rupture in the surrounding spaces or cavities (1).

2. Epidemiology

IA has a prevalence of 1-9% in the global population, with higher rates among Finnish and Asian people and of 2% in patients without any associated risk factors. Unruptured IA are more prevalent with females (3:1) and elderly. When detected in children, boys are more affected than girls and they prevail posterior circulation (40-50%) (2). Factors associated with higher prevalence are **female gender**, **age higher than 30** years old, **nationality** (Chinese, Japanese, Finnish, Korean), **arterial hypertension**, **wall stress**, **genetic factors** (Polycystic kidney, Marfan's disease, Ehlers-Danlos syndrome etc.) and **lifestyle** (smoking, alcohol use, diabetes). (3)

Unruptured IA have 1-2% rupture rate/year (Japanese cohort studies reporting up to a 3.2% rupture rate/year). Subarachnoid hemorrhage (SAH) associated with IA rupture has an incidence of 6-26 cases/100.000 people, with a female male ratio of 1.6:1 and a peak between 40 and 60 years old.

Factors associated with rupture of an unruptured IA are both patient and aneurysm related:

- Patient related: **female gender, arterial hypertension, age (>50-60 years), smoking, sentinel headaches, lifestyle and metabolic factors** as well as **genetic**.
- Aneurysm related: **size, location (basilar bifurcation, anterior and posterior communicating artery), multiplicity, aneurysm growth and multiplicity, clinical symptoms** as well as **inflammation.**

For a ruptured IA, the most important complications are **rebleeding** and **vasospasm**.

Left untreated, a ruptured IA has 20-30% mortality in the first 2 weeks. The risk of rebleeding after a SAH reaches a peak in the first 24h (4.2%) - particularly in the first 6 to 8 hrs., having a cumulative risk of 19% in the first 2 weeks. After 6 months the risk reaches 50% and increases with 3% each year.

In a study conducted in 2013 on 668 consecutive operated aneurysms, Ciurea et al. noted the following incidence of aneurysms: under 16 years - pediatric population - 40 cases (6.1%), 67 (10.4%) cases between 17 and 30 years, 124 cases (19.1%) between 31 and 40 years, 295 cases (45.5%) between 41 and 50 years, 143 cases (21.9%) between 51 and 60 years and 19 cases (3%) over 61 years. The predominantly affected sex is male (68%).

3. Pathology

In terms of pathological findings of IA, **hemodynamic stress** and **arterial wall structure** are often imbalanced. Contrary to what it may be expected, IA are associated with **low shear stress - higher dome-neck ratios** are in turn associated with lower shear stress.

In a normal arterial wall, hemodynamic stress and mechanical injury generates pads of **myointimal hyperplasia**, histologic finding similar with the one found in an IA wall. So, it can be stated that an aneurysm reacts to stress with a high cellular proliferation rate. Another aspect regarding IA is that smooth muscle cell become phenotypically oriented from contraction to proinflammatory and matrix oriented. In comparison with normal artery tissue, there is a high expression and/or activity of **matrix metalloproteinase** (MMP-2 and MMP-9), capable of degrading both elastin and collagen - these findings are correlated with ruptured IA. In addition, although few arterial wall cells undergo apoptosis, in IA there are lots of **apoptotic cell** discovered. This also correlates with the high amounts of inflammatory cells discovered in the IA wall tissue - B and T-cell, macrophages, immunoglobulins, and activated complement fractions (4-6).

Atherosclerotic plaques, often detected in relation with IA, are also highly known to promote inflammation and cell proliferation, hence the relation with apoptosis and often implication in aneurysm rupture.

Familial aggregation of IA highly suggests a genetic role in the development of this disease - this also being the strongest risk factor for SAH. Genetic and functional studies have clearly defined one initiating mechanism - high risk genetic variants may lead to the loss or alteration of THSD1 protein function which in turn may lead to an altered endothelial cell adhesion to the extracellular matrix (4-6).

From a histologic point of view, IA wall tissue displays several characteristics:

- Loss/rupture of the internal elastic lamina
- Myointimal hyperplasia - which leads to intimal thickening
- Muscle fibers disarray
- Depletion of cellular components
- Irregularities in the intimal surface
- Atherosclerotic plaques can be sometimes detected.

4. Etiology

The exact etiology of IA development has not yet been accurately established. IA tend to develop at **arterial bifurcations**, where there is a curve in the parent artery, in the angle described by it and a significant branch artery - in the direction that parent artery would have continued had the curve not been present (8-11).

Various processes, pathologies and genetic factors are to be incriminated:

- Congenital predisposition - a defect in the muscular layer of the arterial wall, often referred to as a medial gap
- Systemic hypertension
- Atherosclerosis
- Embolus - e.g., atrial myxoma
- Infectious - mycotic IA
- Traumatic
- Associated with other conditions - especially as part of genetic syndromes such as Autosomal Dominant Polycystic Kidney Disease, Fibromuscular Dysplasia, Marfan Syndrome, Ehlers-Danlos type IV

Syndrome, Loeys -Dietz Syndrome, Moya Moya Disease or Sickle Cell Anemia.

Location of IA is determined by several conjugate factors. **Saccular IA represents 85%** of all IA and are frequently located on major cerebral arteries - often in the branch apex where the hemodynamic stress on vessel wall peaks (8-11). Fusiform IA tend to develop more in the vertebro-basilar system. The location of saccular IA is as follows:

- **85-95% in carotid system** (anterior circulation), with 3 most common locations
  - Anterior Communicating Artery (ACoA) - 30%
  - Posterior Communicating Artery (PCoA) - 25%
  - Middle Cerebral Artery - 20%
- **5-15% in posterior circulation** (vertebrobasilar)
  - ~10% on basilar artery - basilar bifurcation (basilar tip), basilar-vertebral and basilar-superior cerebellar artery bifurcations as well as anterior inferior cerebellar artery.
  - ~5% on vertebral artery - most common on vertebral-posterior inferior cerebellar artery junction
- **20-30% patients present multiple IA**

5. Clinical Symptoms

IA can be **asymptomatic**, in this case being discovered by chance, or can present as **neurological deficits** or **SAH** - when it ruptures. SAH is the most frequent manifestation of IA, usually being accompanied by intracerebral hemorrhage (IH) – frequently in middle cerebral artery IA, intraventricular hemorrhage (IvH) – frequently in anterior communicating artery IA, basilar tip IA and posterior inferior cerebellar artery IA or even, in 2-5% of the cases, subdural hemorrhage (SH) (4-6) (8-11). Other than major rupture, there are other **"warning signs"** which may lead to IA suspicion:

- Mass effect - brain stem compression, cranial neuropathy or pituitary gland/stalk compression (which in turn leading to endocrine disturbances)
- Sentinel hemorrhage (a minor hemorrhage) - the latency between sentinel hemorrhage and actual SAH is the shortest - ~ 10 days

- Homonymous hemianopia or amaurosis fugax - due to small infarcts or transient ischemia
- Seizures
- Headache
    - around 25% of the patients describe sentinel headache which precedes IA rupture. It can be triggered by aneurysm expansion, partial thrombosis or intramural bleeding.
    - IA rupture is accompanied by "thunderclap headache", often described as "the worst headache of my life", vomiting, neck stiffness and loss of consciousness.
- Cranial neuropathies
    - Oculomotor palsy - extraocular muscle palsy, ptosis and fixed mydriatic pupils
    - Visual loss - due to compressive optic neuropathy (ophthalmic artery aneurysms) which leads to nasal quadrantanopsia, chiasmal compression and facial pain syndromes.

In some particular locations, clinical symptoms may indicate the existence of an IA. In **middle cerebral artery (MCA) aneurysm** the patient may display hemiparesis, visual field impairment as well as epileptic seizures. Moreover, in **posterior cerebral artery (PCA) or vertebral artery (VA)** clinical examination may detect oculomotor palsy and brain stem compression while in **aneurysms of cavernous part of internal carotid artery (ICA)** patient may develop cavernous sinus syndrome (ophthalmoplegia, proptosis, ocular and conjunctival congestion, trigeminal sensory loss and Horner's syndrome).

For a more uniform evaluation of these patients as well as for a prognostic evaluation, the most used scale is the one proposed by Hunt and Hess – grade 0 represents an unruptured IA while clinical symptoms generated by ruptured IA are graded from 1 to 5.

Table 1. Hunt and Hess Classification

Grade 0	Unruptured IA
Grade I	Asymptomatic / Minimal Headache / Slight nuchal rigidity
Grade II	Moderate to severe headache/Nuchal rigidity/Cranial nerve palsy
Grade III	Drowsy/Confused/Mild focal deficit
Grade IV	Stupor/Moderate to severe hemiparesis/Possible early decerebrate rigidity and vegetative disturbances
Grade V	Deep coma/decerebrate rigidity

Patients with Hunt&Hess grade IV and V do not have surgical indication. For Hunt&Hess III, immediate surgical intervention is possible only when specific operating room and anesthetic equipment is available. Hunt&Hess grades I and II are compatible with an immediate surgical intervention.

6. Investigations

The "golden standard" in terms of IA diagnosis is **Digital Substraction Angiography (DSA)**, although angiographic sequences of CT and MRI are rapidly gaining ground. However, despite still being the primary diagnostic tool, DSA has a risk of transient ischemic stroke (TIS) (1%), inguinal hematoma (1-2%) and stroke (0.01%).

Angiographic CT has a sensitivity and specificity of 96-98%, varying for IA < 3mm to 90-94% reaching up to 100% for IA > 4 mm. The main advantage of angiographic CT is its low duration as well as bony structure visualization. On the other hand, the drawbacks are lack of sensitivity for IA in the skull base and cavernous sinus which fills with contrast substance. A widely used system of grading SAH on CT scans was proposed by Fisher and co-workers but is best modified to make it useable with current imaging.

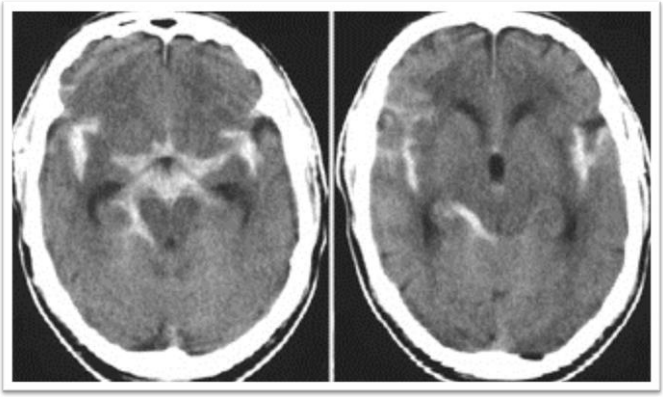

Figure 3. CT Scan on a patient with SAH.
(Personal collection of Professor AV Ciurea and Assistant Professor AG Mohan)

Table 2. Fisher Scale

Grade 1	**No SAH**
Grade 2	A thin layer of subarachnoid blood less than 1 mm thick
Grade 3	Focal or diffuse thick subarachnoid blood more than 3 mm thick
Grade 4	Intracerebral/intraventricular blood with or without subarachnoid blood

Angiographic MRI has 70-99% sensitivity and 100% specificity. Most frequently, physicians use the three-dimensional time of flight sequence (3D TOF). Its cons are represented by increased duration of image acquisition and high sensitivity to movement.

Lumbar puncture is indicated only when the event happened at least 3 days prior to hospital admission or in case of angiography CT showing no evidence of IA despite clinical manifestations. Lumbar puncture analysis detects red blood cells in the cerebral spinal fluid (CSF) and xanthochromia (7).

7. Treatment

HSA is a major medical and neurosurgical emergency and diagnostic measures should be applied immediately. Once the diagnosis of HSA has been established by CT-scan or DSA, the patient must be urgently referred to a center that has the surgical means to intervene in such a pathology (operating microscope, specialized ICU unit, etc.). **Nimodipine therapy** (dihydropyridine calcium channel blocker) should be initiated **1-2 mg / h - up to 5 mg** to prevent vasospasm and a **preoperative angiography (DSA) should be performed to examine all aneurysms**.

Treatment approaches for IA have radically shifted since the increasingly adoption of endovascular therapies. Hence, the debate whether open microsurgical approach or endovascular techniques is better suited became a popular topic in the field of vascular neurosurgery. The decision must be individualized, taking into account not only aneurysm characteristics, rupture risk but also patient status and preferences (7).

Endovascular techniques display a wide range of options that physician can choose from:

- Coils
- Stent assisted treatment - vascular stents and coils (Neuroform and Enterprise stent); it provides a desynchronization between arterial pulse of originating artery and IA, it consolidates the originating artery and promotes intimal cell proliferation and growth along the IA neck.
- Single vascular stent (in some cases even double stents are used).
- Blood flow diverter stent (PED - pipeline embolization device) - it reduces the amount of blood flow which reaches the IA, promoting aneurysm thrombosis
    - This type of endovascular device showed promising results in two major studies. Pipeline embolization device for IA treatment (PITA) showed 93.3% complete aneurysm occlusion at angiographic follow-up (12), while Pipeline for uncoilable or failed IA (PUFS) showed a 99.1% successful device placement rate on internal carotid artery, petrous

segment (which is often inaccessible for open microsurgical approach) (13).

At the opposite end, the **open microsurgical approach** is based primarily on vascular clips that fully obliterates the aneurysm from circulation - there are various clips models (McFadden VariAngle, Yasargil, Harnesniemi, Sugita). ***7.1. Unruptured IA***

There is a high amount of controversy regarding the proper treatment decision of unruptured IA - which need to be treated, and how, and which to be observed.

A study on 2351 patients - 451 treated with endovascular methods and 1900 surgically operated, revealed a perioperative mortality of 1.8% with surgery and 2% with endovascular methods. However, at 1-year follow-up the surgical operated patients have a 12.6% mortality compared with 9.8% of the endovascular group (14). Age and aneurysm characteristics (dimensions, shape) were determined as perioperative mortality and morbidity factors. Moreover, age > 50 years, IA > 12 mm, posterior location, history of stroke and clinical symptoms were predictors of a negative outcome.

A retrospective cohort study on 2600 patients showed that perioperative mortality and discharge to a neurorehabilitation facility were higher among surgically treated patients rather than the ones treated by endovascular means - 18.5% compared to 10.6% (7).

California University Report paralleled the aforementioned conclusion, reporting perioperative complications in 25% (surgical approach) versus 10% (endovascular approach) (7).

A meta-analysis showed that clipping resulted in a significantly more disability in contrast with coiling. However, this proved to take place only in the short term (0-6 months), while on the long term the outcome was similar. Additionally, mortality (in-hospital and overall), hemorrhage as well as infarction were no different among the two categories (15).

Lawson and colleagues compared the risk of coiling and clipping against the natural rupture risk mortality. Their results showed an overall mortality rate of 2.66% for clipping and 2.17% for coiling as well as differences in outcome - 4,75% for the clipping group and 2.16% for the endovascular treated one. Overall, the analysis demonstrated that

clipping is suitable for small, unruptured aneurysm in patients younger than 61-70 years old while coiling should be considered for small unruptured IA in patients older than 70-80 years (16).

Age was also studied as an outcome predictive factor. Poor neurological outcome related with treatment option and perioperative and in-hospital mortality as well as morbidity did not significantly differ among patients 65 years old and younger but showed higher results in patients older than 65 years old - 19% for surgically operated patients compared to 8% in the endovascular group (17,18).

Hospital costs is another criteria worth comparing these procedures on, clipping showing higher initial scores which in 2 to 5 years showed no difference from the coiling method, mainly because of the angiographic follow-up and outpatient costs (19).

Although there are arguments in favor of endovascular approach for unruptured IA, supported by lower perioperative mortality and morbidity rate as well as better postoperative outcome, there are several aspects to be further considered. Studies show that endovascular techniques result in 50-70% cases of total IA occlusion and an almost complete occlusion (90% occlusion) in 90% of the cases. However, imagistic findings showed that in 32% of cases there is residual aneurysm, progressive thrombosis rate of 25% and a global rate of recurring varying from 49% to 90% in case of giant IA. The "gold standard" procedure for unruptured IA is still traditionally considered to be clipping by microsurgical approach as it completely excludes the aneurysm from the circulation and has lower reintervention rates (7).

7.2. Ruptured IA

One of the most important studies to evaluate safety and efficiency of the two approaches is International subarachnoid aneurysm trial (ISAT), a randomized trial conducted on 2143 patients - 1070 in the clipping group and 1073 in the coiling group. It aimed to determine poor outcome (modified Rankin Score (mRS) = 3-6) at 1 year follow-up. 97.3% of total IA were located in the anterior circulation (ACoA - 50.5%, ICA - 32.5%, MCA - 14.1). The results at 1 year follow-up showed that 23.7% of coiled treated patients and 30.6% of clipped patients met the aforementioned outcome (mRS = 3-6). Additionally, rebleeding rate at 1

year was 0,15% for endovascular approach and 0.07% for surgical approach (20).

The Barrow Ruptured Aneurysm Trial (BRAT), also a randomized study, had mainly the same aim as the previous one, mainly to determine safety and efficiency of these 2 methods. There were 239 patients surgically treated and 233 treated using coils. At 1 year follow-up, poor outcome (mRS = 3-6) was observed in 33.7% of the patients surgically treated compared with coiling techniques which resulted in just 23.2% poor outcome. Probability of reintervention was 4.49% with clipping while for coiling it reached up to 10.6% (more than twice as much). At 3-year follow-up, IA located on the posterior circulation proved to have a better outcome if treated by endovascular techniques. Reintervention rate at this point was 5% for clips and 13% for coils. During the same 3-year interval, complete thrombosis of aneurysm went initially from 85% to 87% for clips while it dropped from 58% to 52% for coils. At 6 years follow-up the occlusion rate was 96% for clips compared to 48% for coils. Overall, the reintervention rate was calculated at 4.6% for clips and 16.4% for coils. It is worth mentioning that surgical approach showed more versatility than endovascular one as approximately 30% of IA were inoperable by endovascular approach so the neurosurgeons opted for open microsurgery (21).

A Chinese study conducted by Li and colleagues, presented results on 192 randomized patients. Cerebral infarction rate was measured reaching 21.7% for clips and 12.8% for coils, while aneurysm occlusion was 83.7% for clips and 64.9% for coils, both parameters measured at 1 year follow-up (22).

Two meta-analysis conducted by Lanzino and his colleagues and Li et al. have also offered conclusive results. The first one showed that poor outcome at 1 year follow-up was higher in the surgical group rather than embolization one, with no mortality difference detected among the two. In the first month after treatment, rebleeding rates were lower in the coiling group [23]. Li and colleagues demonstrated the same results as the previous meta-analysis regarding poor outcome, a rebleeding rate of 1% for clips and 2-3% for coils and occlusion rates of 84% for clips and 66.5% for coils. They also found that vasospasm proved to be more common after clipping (43.1%) than coiling (43.1%) (24).

Another study further researched treatment associated vasospasm and observed the patient who undergo clipping developed localized vasospasm (around the rupture site) while those treated by endovascular approach demonstrated progressive distal vasospasm (25).

For ruptured IA, it can be stated that although short term results are promising for endovascular approach, also proving to determine less perioperative complication, mortality and morbidity rate, in the long term those parameters are similar with the neurosurgical approach. However, clips still remain more efficient in terms of occlusion, rate of thrombosis and rebleeding prevention, especially on longer periods of time. Taking everything into account, further indications ca be made regarding the appropriate choice of treatment:

Clips	**Coils**
Hematoma Evacuation	H&H score > 2
Young age	Cerebral Edema
Wide IA neck	Anticoagulant treatment already administered
MCA aneurysm	Posterior IA location
Complex/unfavorable anatomy	Dome: neck ration > 2
Sinuous artery	Fusiform IA
	Multiple IA

Surgical timing is another aspect worth focusing on. It is divided into 4 categories:

- Immediate surgery (< 24h)
- Early surgery (24 – 72h)
- Delayed (3-10 days post SAH)
- Late surgery (10-14 days post SAH)

Immediate IA obliteration can improve outcome by eliminating rebleeding, especially for endovascular treatment, representing the actual approach. In a single center study, it was concluded that patients treated in the first 24h had lower incidence of poor outcome compared with those operated on after 24h. Moreover, there was also an absolute risk reduction in poor outcome and death if coiling can be performed in the first 24h [25,26]. However, immediate surgery is not recommended for multiple aneurysms in a single stage procedure, giant aneurisms, poor medical condition, posterior circulation aneurysms and low vascular surgery experience.

Delayed surgery is preferred for more complex lesions such as giant IA or in cases for which prolonged periods of temporary occlusion are expected to achieve aneurysm occlusion.

In conclusion, earlier IA occlusion has reduced the impact of rebleeding on patient's outcome, for both surgical and endovascular techniques. Additionally, it also allows more aggressive and earlier management of cerebral vasospasm (27).

8. Surgical technique

The choice of best treatment depends on patient clinical presentation, aneurysm anatomy, neurosurgeon's experience, the endowment of the neurosurgical department. Surgical clipping of the IA neck or occlusion of the IA dome with metal spirals (GDC: Guglielmi Detachable Coils) inserted endovascularly, are currently the methods of choice in the treatment of most aneurysms.

The current approach in surgical practice requires microsurgical dissection and clipping of the aneurysmal neck. In Romania, this technique was introduced by Professor Leon Dănăilă, with the first aneurysm operated microsurgically on January 26, 1979 and with a consecutive series of 2854 patients with intracranial aneurysms operated until the end of 2007 (Dănăilă et.al.). Preoperative mortality with this technique decreased to 3% (Ciurea et.al.).

Aneurysmal surgery aims to prevent the rupture or increase in size of the aneurysm, while keeping all normal vessels intact and minimizing damage to brain tissue and cranial nerves. **Surgical morbidity** is determined by several factors, including the **location**, **size** and

aneurysm anatomy, the **patient's neurological and medical condition** as well the **coexistence of other complications of HAS**. Placing the clip too low (towards the neck) on the vessel leads to obstruction of the carrier vessel, while placing it too high (towards the apex of the aneurysm) leaves an aneurysmal remnant in place with a risk of subsequent rupture.

The surgical approach must be performed under the operating microscope. The dissection of the carrier vessel is done patiently with the help of fine dissectors. Experienced surgeons can use microscopic hooks, faceted take-offs or even syringe needle tips. These tools are very sharp and are used by surgeons dedicated to the vascular field. Their use is contraindicated for surgeons with little experience in this field. Once the aneurysm neck is found, the dissection ceases. The apex of the aneurysm will not be exposed in any form (only if a hematoma needs to be aspirated). Two temporary safety clips are applied – one upstream and one downstream of the aneurysm, after which the actual aneurysm package is clipped. Different combinations of clips can be made depending on the anatomy of the area and the size of the aneurysm. After applying the final clip to large or giant aneurysms, a discreet electrocoagulation can be applied to reduce their volume and compressive nature. Temporary clips are removed as soon as possible and biomaterials for hemostasis are applied. Irrigate the operating field – 2 liters of saline and monitor the character of the serum in the field. Once the serum is clean, the dura mater can be closed, the bone flap positioned and the skin sutured. The sutures are suppressed at 7 days and the patient must be mobilized at 12-24 hours. Avoid cold exposure and hypertension.

9. Post-operative care

Most patients will need to be monitored in the intensive care unit (**ICU**). Although the optimal duration of monitoring in intensive care has not been studied, **monitoring of intracranial pressure**, **hemodynamic parameters**, **intravascular volume**, **lung function status** and **vasospasm prevention** may require long-term stay in intensive care. Sequential CT scans may be needed to differentiate neurological degradation caused by vasospasm, hydrocephalus, or

cerebral edema. A rehabilitation program is often recommended for patients recovering from HAS due to the variety of motor, cognitive, speech, and psychosocial deficits that may occur.

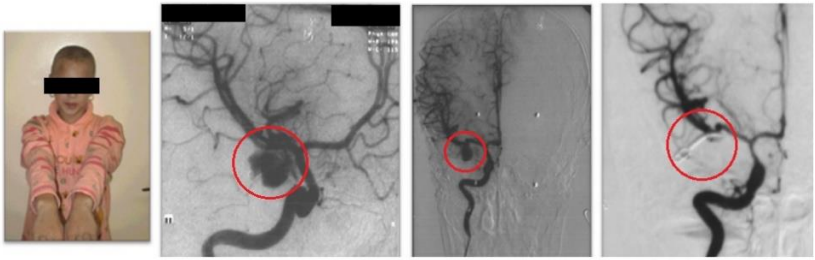

Figure 4. Pre and postoperative images after surgical approach of an IA in a 13-year-old patient.
(Personal collection of Professor AV Ciurea and Associate Professor AG Mohan)

10. Biocompatible materials used for the treatment of aneurysms

10.1. Aneurysmal clips

The first to propose the idea of a vascular clip was Professor Harvey W. Cushing (the father of modern neurosurgery) who improvised a series of "clips" from wire office clips - sterilized and then used for hemostasis in the operating field. Silver or surgical steel clips under various variants followed (McKenzie, Olivecrona, Perneczky, etc.) which were a real progress in IA occlusion.

Yet, the best-known clips are the Yasargil clip (the most important - with its subtypes) and the Sugita clip (with its subtypes). Non-ferromagnetic clips with MRI safety up to 3 Tesla are currently used to make postoperative MRI evaluation possible. Once applied, these clips can no longer be repositioned. The introduction of microsurgery totally changed the vision of the direct aneurysmal approach, on which occasion the aneurysmal exclusion clips were modified.

10.2. Other types of devices used in vascular neurosurgery

10.2.1. Coils

GDC: Guglielmi Detachable Coils) are used in endovascular aneurysmal pouch occlusion. The catheter inserted through the

femoral puncture is directed to the aneurysm package and a wire inserted through the catheter enters the aneurysm by pushing and handling properly. This thread wraps (spirals) inside the aneurysmal sac obstructing it.

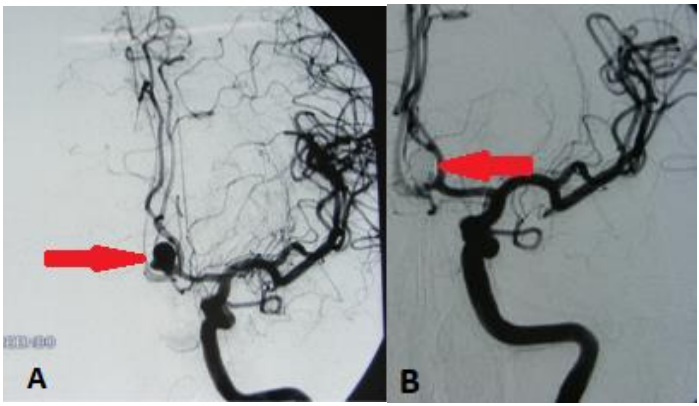

Figure 5. Angiography of AcoA aneurysm. A. Preoperative view; B. Postoperative view with coils
(Personal case of Prof. Dr. AV Ciurea)

10.2.2. Stents

The stents have a perforated cylinder structure of a metal network that is inserted endovascularly into the lumen of the vessel at the level of a stenosis. Dilation of the cylinder with a balloon or simple release of the stent with shape memory determines its expansion with the correction of stenosis.

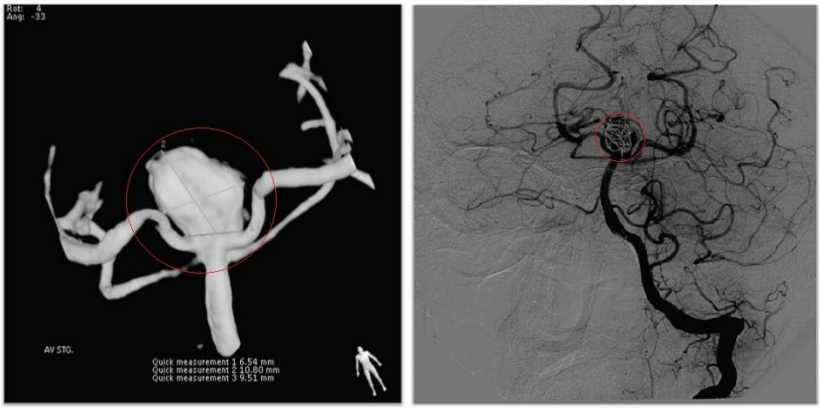

Figure 6. Endovascular treatment of a giant basilar artery aneurysm. (Personal collection of Professor AV Ciurea and Assistant Professor A Chefneux)

11. Aneurysmal subarachnoid hemorrhage prognosis

Following aneurysmal rupture, the sudden death or patient's death prior to reaching a medical unit occurs in 30-50% of cases. The total mortality under the current treatment conditions is on average 45% (ranging between 32-67% in various statistics) (Poeata et.al.) especially due to severe HSA (H&H grade IV and V) and due to complications (repetition rupture, vasospasm, etc.). Approximately 30% of survivors have moderate and severe dysfunctions (Poeată, Dănăilă, Ciurea et al., 2011).

In the study published by Ciurea et al. in 2006 out of 428 cases of ruptured intracranial aneurysms operated on, patients' condition assessed on the Glasgow Coma Outcome (GOS) scale, at three months postoperatively, the results were as follows: good recovery (GR) - 278 cases (64.9%), moderate disability (MD) - 101 cases (23.6%), severe disability - 21 cases (5%), persistent vegetative states - 5 cases (1.1%) and deaths - 23 cases (5.3%). Currently (2014) the percentages are improving due to the existence of clinics with great experience, collaboration with neurology and last but not least, the latest generation technique is added.

12. Conclusions

IA represents a neurosurgical emergency, a life threatening pathology due risk of rupture and vasospasm development. Subarachnoid hemorrhage (SAH) associated with IA rupture has an incidence of 6-26 cases/100.000 people, with a female male ratio of 1.6:1 and a peak between 40 and 60 years old. Rupture mortality reaches up to 40% while only 30% of patients can fully recover. Main treatment options are represented by neurosurgical clips and endovascular coils, the former becoming increasingly popular.

For ruptured IA, it can be stated that although short term results are promising for endovascular approach (coils), also proving to determine less perioperative complication, mortality and morbidity rate, in the long term those parameters are similar with the neurosurgical approach. However, clips still remains more efficient in terms of occlusion, rate of thrombosis and rebleeding prevention, especially on longer periods of time. Taking everything into account, further indications ca be made regarding the appropriate choice of treatment. Clips are most suited for younger patients, IA with wide neck and located on MCA, when there is also a hematoma which needs to be evacuated, complex/unfavorable anatomy as well as sinuous arteries. Coils indications include H&H score > 2, cerebral edema, patient already receiving anticoagulant treatment as well as posteriorly located IA, dome:neck ratio > 2, fusiform and multiple IA.

Abbreviations:

IA – intracranial aneurysm, **SAH –** subarachnoid hemorrhage, **CVS –** cerebral vasospasm, **DSA** - Digital Substraction Angiography, **CT** - Computed Tomography, **MRI** - Magnetic Resonance Imaging, **WFNS** - World Federation of Neurosurgical Societies, **ACoA** - Anterior Communicating Artery, **PCoA** - Posterior Communicating Artery, **MCA** - Middle Cerebral Artery, **IH** - intracerebral hemorrhage, **IvH** - intraventricular hemorrhage, **SH** - subdural hemorrhage.

Disclaimer: the authors declare no conflict of interests.

References:

1. Bhidayasiri, Roongroj; Waters, Michael F.; Giza, Christopher C. (2005). Neurological differential diagnosis : a prioritized approach (3. Dr. ed.). Oxford: Blackwell Publishing. p. 133. ISBN 978-1-4051-2039-5.
2. Lall RR, Eddleman CS, Bendok BR, Batjer HH. Unruptured intracranial aneurysms and the assessment of rupture risk based on anatomical and morphological factors: sifting through the sands of data. Neurosurg Focus. 2009;26(5):E2.
3. Winn HR. Section 12. Chapter 377. The natural History of Cerebal Aneurysms; p3207-3220. In Youmans and Winn. Neurological Surgery, 7th Edition. Elsevier 2017.
4. Constantinovici A., Ciurea A.V., Ghid practic de neurochirurgie, Editura Medicală, Bucuresti, 1998.
5. Ciurea A.V., Tratat de Neurochirurgie Vol. 1, Editura Medicală, București, 2010.
6. Ciurea A.V., Tratat de Neurochirurgie Vol. 2, Editura Medicală, București, 2011.
7. Ellenbogen RG, Sekhar NL, Kitchen N. Chapter 16. General Principles of Treatment in Ruptured and Unruptured Intracranial Aneurysm; p.254-263. In: Principles of Neurological Surgery. 4th Edition. Elsevier 2018.
8. Dănăilă L., Vascularizația arterială şi venoasă a creierului, Editura Tipart Group, 2001.
9. Dănăilă L., Arsene. D., Carp N., Atlas de patologie chirurgicală a creierului (Atlas of Surgical Pathology of the Brain), Editura Moonfal Press Bucharest, (ed. I 2000, ed. II 2001).
10. Dănăilă L., Pais V., Stefănescu F., Cerebrovascular malformations - an atlas of histopathology and ultrastructure, Editura Cartea Universitară Bucureşti, 2005.
11. Dănăilă L., Stefănescu F., Anevrismele cerebrale, Editura Academiei Române, București, 2007.
12. Nelson PK, Lylyk P, Szikora I, Wetzel SG, Wanke I, Fiorella D. The pipeline embolization device for the Intracranial treatment of aneurysms trial. AJNR Am J Neuroradiol. 2011;32(1):34-40.
13. Becske T, Kallmes DF, Saatci I, et al. Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. Radiology. 2013;267(3):858-868.

14. Wiebers DO, Whisnant JP, Huston J 3rd, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;362(9378):103-110.
15. Hwang JS, Hyun MK, Lee HJ, et al. Endovascular coiling versus neurosurgical clipping in patients with unruptured intracranial aneurysm: a systematic review. BMC Neurol. 2012;12:99. Published 2012 Sep 22.
16. Lawson MF, Neal DW, Mocco J, et al. Rationale for treating unruptured intracranial aneurysms: actual analysis of natural history risk versus treatment risk for coiling or clipping based on 14,050 patients in the Nationwide Inpatient Sample database. World Neurosurg. 2013; 79:472–478.
17. Mahaney KB, Brown RD,Jr, Meissner I, et al. Agerelated differences in unruptured intracranial aneurysms: 1-year outcomes. J Neurosurg. 2014; 121:1024–1038.
18. Brinjikji W, Rabinstein AA, Lanzino G, et al. Effect of age on outcomes of treatment of unruptured cerebral aneurysms: a study of the National Inpatient Sample 2001-2008. Stroke. 2011; 42:1320–1324.
19. Lad SP, Babu R, Rhee MS, et al. Long-term economic impact of coiling vs clipping for unruptured intracranial aneurysms. Neurosurgery. 2013; 72:1000–11; discussion 1011-3.
20. Molyneux AJ, Kerr RS, Yu LM, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet. 2005;366(9488):809-817.
21. McDougall CG, Spetzler RF, Zabramski JM, et al. The Barrow Ruptured Aneurysm Trial. J Neurosurg. 2012;116(1):135-144.
22. Li ZQ, Wang QH, Chen G, et al. Outcomes of endovascular coiling versus surgical clipping in the treatment of ruptured intracranial aneurysms. J Int Med Res. 2012; 40:2145–2151.
23. Lanzino G, Murad MH, d'Urso PI, et al. Coil embolization versus clipping for ruptured intracranial aneurysms: a meta-analysis of prospective controlled published studies. AJNR Am J Neuroradiol. 2013;34:1764–1768.
24. Li H, Pan R, Wang H, et al. Clipping versus coiling for ruptured intracranial aneurysms: a systematic review and meta-analysis. Stroke. 2013;44:29–37.

25. Jones J, Sayre J, Chang R, et al. Cerebral vasospasm patterns following aneurysmal subarachnoid hemorrhage: an angiographic study comparing coils with clips. J Neurointerv Surg. 2015; 7:803–807.
26. Phillips TJ, Dowling RJ, Yan B, et al. Does treatment of ruptured intracranial aneurysms within 24 hours improve clinical outcome? Stroke. 2011;42:1936-1945.
27. Le Roux P, Elliott JP, Newell DW, et al. The incidence of surgical complications is similar in good and poor grade patients undergoing repair of ruptured anterior circulation aneurysms: a retrospective review of 355 patients. Neurosurgery. 1996;38:887-895.
28. Winn HR. Section 12. Chapter 379. Surgical Decision Making for the Treatment of Intracranial Aneurysms; p3232-3256. In Youmans and Winn. Neurological Surgery, 7th Edition. Elsevier 2017.

INTRACRANIAL CAVERNOMAS

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Contents

1. General data

1.1. Historic

Vascular malformations of the central nervous system have been described in the literature since the 17th century, but the cavernous cerebral malformations have been described only since the 19th century. (1)

This pathology is included in the current medical nomenclature with different names: cavernous angioma, cavernous hemangioma, cavernoma or cavernous malformation. Initially, the terms „cavernous angioma" or „cavernous hemangioma" were used, but these were replaced with „cavernous malformations" or „cavernoma" in order to differentiate from the vascular neoplasic lesions suggested by the term „angioma". (2)

Intracranial cavernoma is mentioned for the first time in the literature in 1854, in a publication of the German anatomist Hubert von Luschka (1829-1875). He describes postmortem a tumor of vascular nature, asymptomatic, localized in the left frontal lobe of a 40-year-old patient.

However, the term of „cavernous angioma" is used in the literature 8 years before Luschka, in 1846 by Carl von Rokitansky (1804-1878), to describe a cerebral lesion of vascular nature. Later, in 1863, Rudolf Virchow (1821-1902) describes the histopathological structure of a cavernoma for the first time. [3]

The first surgical resection of an intracranial cavernoma was performed by Bremer and Carson in March 1890 on a 23-year-old patient who had a 3-year history of partial seizures involving the left side of the body. After surgery, the symptoms remitted completely. (4)

The first general presentation of this pathology was realized by Walter Dandy (1886-1946) in 1928. He presented a series of 5 operated cases and collected another 44 cases from all the literature until the year of the publication. He described the microscopic and macroscopic features of cavernomas and the clinical signs (predisposition to bleeding, focal neurological deficits and the most common sign: epilepsy). (5)

Krayenbuhl and Yaşargil (1957) publish a study of all cavernomas cases existent in the literature. Until then, only 82 cases were known globally. [6] Since the study published by Walter Dandy in 1928 until this study the number of cases has increased by only 38.

The modern era in the detection and treatment of cavernomas is marked by the introduction of CT (1971), MRI (1977) and the operating microscope (1957) in the current medical practice. (7),(8)

In 1976, a study published by Voigt K. and Yaşargil G shows that there are 164 cases of cavernomas in the literature, so the number of cases has doubled in just 19 years. [9] This increase in the number of diagnosed cases is due to the introduction of CT and especially MRI scans in the usual neurosurgical diagnosis methods.

1.2. Epidemiology

Cerebral cavernomas are a rare pathology of the central nervous system and are defined as „cryptic angiographic lesions, classically defined as dilated vascular structures, with thin walls located in the central nervous system, without cerebral parenchyma interposed". (2)

Cavernomas are one of the four vascular malformations that can form in the central nervous system and represent 5-10% of all vascular malformations. They have an incidence of 0,39%-0,47% in the general population. [10] Before using the modern imagery (CT, MRI), cavernomas were most commonly detected by surgical exploration or autopsy.

Most of the cavernomas are symptomatic between the 2nd and 5th decades of life. (11)

There are no differences in the incidence of cavernomas between sexes.

1.3. Genetics and morphology

Cavernomas can either have a spontaneous or familial form. The spontaneous form is characterized by isolated cases, most of them unique lesions. In the familial form there are multiple lesions which grow both in size and number, in the context of a family with neurological disorders. (2)

The literature speaks about the existence of an autosomal dominant pattern of genetic transmission with incomplete penetrance which is caused by a mutation in the CCM1/KRIT1, CCM2/MGC4607 and CCM3/PDCD10 genes. However, about 5-15% of all familial cavernomas cannot be explained by the presence of these 3 genes, suggesting the existence of an additional locus for CCM genes. (11)

According to McCormick's 1966 classification, neurovascular malformations can be divided into 5 categories: (1)

- Telangiectasias
- Varicose veins
- Cavernous malformations
- Arteriovenous malformations (AVM)
- Venous angiomas

Later, this classification was modified: the varicose veins were combined with venous malformations/venous angiomas and they formed together another category, development venous anomaly (DVA). In literature, there are cases of coexistence of those malformations. The most common malformation associated to cavernomas is DVA. Another common combination is capillary telangiectasia. (7)

Macroscopically, cavernomas are well defined lesions, with a multilobed, berry-like red-purple appearance, that contain hemorrhages in different stages of evolution (even calcifications). (2). These lesions can be single or multiple, ranging in size from 1 mm up to more than 4 cm. In literature, there are some rare cases with cavernomas that affect an entire cerebral lobe or even more. (7)

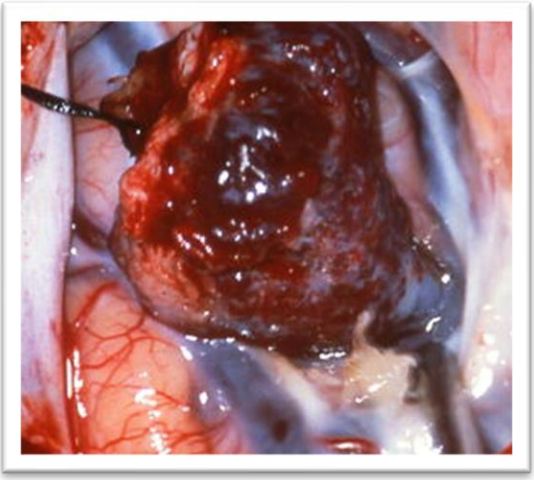

Figure 1. Intraoperative view of intracerebral cavernoma (Personal collection Prof. Dr. AV Ciurea)

In a typical case, the nucleus of the lesion has sinusoids of different sizes, filled with blood and separated by thin fibrous fascicles. The blood can be coagulated due to thrombosis and the nervous tissue near the lesion is typically discolored due to repeated microhemorrhages which led to an accumulation of red blood cells degradation products. (7)

Microscopically, cavernomas are sinusoidal structures with thin walls of collagen, lined with a single layer of endothelium. Outside the lumen are macrophages which contain iron and hemosiderin. Electron microscopy reveals that the endothelium is fragile and can be fenestrated or spaces can be formed at the intercellular junctions. All these changes are the results of a malfunctioning blood-brain barrier at this level. (2), (7)

From a histopathological standpoint, 3 subtypes of cavernomas have been identified: the cystic form, the calcified form and dural-based cavernoma. (7)

1. The cystic form:
    - Usually located in the posterior fossa
    - It is more frequent in women and elderly
    - It is predisposed to bleeding and increasing in size
    - It is a rare form. By 2010, only 25 cystic forms of cavernomas have been identified (12)
    - The mechanism of formation is not completely elucidated
2. Dural-based cavernoma
    - Usually located in the middle fossa, adjacent or in the cavernous sinus, in the cerebellopontine angle or on the tentorium
    - Has a clinically aggressive natural course
    - If the lesions located in the middle fossa are abundantly vascularized, they tend to bleed profusely during surgical excision.
3. The calcified form:
    - Usually located in the temporal lobe
    - It is severely calcified

- The risk of bleeding is very low
- It is very epileptogenic.

1.4. Location

Intracranial cavernomas can be located infratentorial or supratentorial. The most frequent location is suprantentorial and represents about 73% of cases. Most of them are located in the cerebral white matter, affecting the lobes in the following order: frontal, parietal, temporal and occipital lobe. Epileptic seizures appear most frequent in supratentorial seizures locations (53%), representing the main symptom in these cases. Most of these lesions are located in non-eloquent areas and aren't diagnosed until the first epileptic seizure. (2)

Infratentorial cavernomas can be located in the cerebellum or, more commonly, in the brainstem, in the following order: pons, midbrain and medulla oblongata. Infratentorial cavernomas become symptomatic easily and at smaller sizes than the supratentorial ones and are more severe, starting with focal motor deficits in more than 60% cases. (13)

1.5. Natural evolution

The natural evolution of cavernomas is a strong decision factor in the management of this pathology. We must evaluate the mortality risk due to recurrent bleeding, mass effect or epileptic seizures.

In general, cavernomas are benign. Death is very rare and is caused by the profuse bleeding secondary to a big lesion that affects eloquent areas of the cortex. Compared to other cerebral vascular pathologies, cavernomas are rarely responsible for massive bleeding and very rarely for subarachnoid or intraventricular hemorrhage. (2)

Cavernomas develop slowly and the symptoms are caused most often by the mass effect induced by them on the adjacent structures. Untreated, they tend to bleed. The risk of bleeding is low until the first bleeding (0,25% per patient per year 0,1% per lesion per year). After the first hemorrhage, the risk of recurrence increases significantly (annual bleeding rate about 1,6-3,1%). (14), (15), (16)

The diversity of terms used in literature to describe the hemorrhage from cavernomas suggests that this type of hemorrhage is very different from the one secondary to other cerebral lesions of vascular origin: symptomatic hemorrhage, subclinical hemorrhage, clinically significant

and radiologically identifiable bleeding, radiologically unidentifiable bleeding, microhemorrhage, bleeding in the sinusoidal space of the malformation. However, the hemorrhage due to cavernomas is rarely massive and sometimes is difficult to be radiologically identified. (2)

The location of the cavernomas is the most important factor required to predict the probability of a patient`s state getting worse (deep supratentorial lesions have a bleeding rate up to 10% per year). (2)

Supratentorial cavernomas are an important cause of epileptic seizures, especially in the first 4 decades of life. The increase in the number of epileptic seizures can be explained by the irritating effect on the cerebral cortex caused by the process of gliosis and by the perilesional hemosiderin deposits. (2)

2. Clinical presentation

The clinical presentation of cavernomas varies a lot due to size, localization and tendency to bleed. Over the time the symptoms can vary widely from periods of exacerbation to periods of remission. In some rare cases, cavernomas can simulate multiple sclerosis due to progressive fluctuation of neurological deficits. (17)

There are asymptomatic forms, which can be discovered on CT or MRI performed due to a headache or post-traumatic or post-mortem after an intracranial hemorrhage. The asymptomatic patient represents approximately 15-20% of cases. (2)

Classically, cavernomas can have 3 clinical signs: comitial crises, focal neurological deficits and bleeding. These can be present either individually or in various combinations. 25-30% of cases can have nonspecific symptoms such as tinnitus, vertigo or headache. (18)

Partial or generalized **comitial seizures** appear at 41-80% of patients, representing the most frequent clinical symptom of supratentorial cavernomas. The annual cumulated risk of these patients to have a new crisis is estimated between 1,34-2,8%. Comparing to other pathologies, the incidence of comitial crises is double: in MAV 20-40% and in gliomas 10-30%. (7)

Cavernomas do not invade the parenchyma and are not intrinsically epileptogenic. The seizures appear due to the perilesional iron deposits in the adjacent brain parenchyma combined with the inflammation and

the glial changes, as evidenced by laboratory studies. Iron ions help to produce free radicals and lipid peroxides, which affects the function of cellular receptors. These events lead a marked increase of excitatory neurotransmitter amino acids. (7)

Compared to other vascular malformations, the comitial crises associated with cavernomas are more resistant to medication. About 4% of partially treatment-resistant epilepsy is caused by cavernomas. (19)

The comitial seizures are variable with the location of the lesion, size, bleeding history and patient's age. Therefore, cavernomas from the temporal lobe produce more frequently drug-resistant epileptic seizures. (20)

An intracranial cavernoma does not necessarily lead to the onset of comital crises. The patients with supratentorial lesions can be asymptomatic until bleeding occurs or until an environmental factor causes the epileptic activity. Patients with similar locations, sizes and radiological presentations of the lesion may have completely different seizures. This variability is more obvious in patients with multiple cavernomas, where any lesion has an epileptogenic risk. (7)

Focal neurological deficits usually appear when the lesions affect the motor cortex, speech areas, basal ganglia, brainstem or spinal cord. About 30-50% of patients have sensory and motor deficit, dysphasia and cranial nerves damage. Cavernomas rarely produce a rapid worsening of the patient's condition due to their small size and slow growth. A rapid worsening may occur in case of a secondary bleeding in the adjacent parenchyma, that leads to its compression and destruction. (7), (13)

The intracerebral hemorrhage is a very well-known phenomenon which appears secondary to cavernomas. Usually, the bleeding is well tolerated depending on the volume, adjacent to the eloquent areas, the patient's age, but there are some cases, very rare, when it can be fatal. Hemorrhage caused by cavernoma has been divided into 2 categories: intralesional hemorrhage and extralesional hemorrhage. (7)

Intralesional or encapsulated hemorrhage is limited to the edge of the cavernoma and leads to the enlargement of the cavernoma. The hemorrhage is delimited by the parenchyma adjacent to the wall of the cavernoma. Most likely, the hemosiderin-rich adjacent parenchyma has a role in preventing the spread of blood in the healthy parenchyma. The

result is that a capsule is formed which attracts fluid through osmosis and leads to the enlargement of the lesion. (7)

Extralesional hemorrhage extends beyond the hemosiderin ring. It presents signs of acute or subacute bleeding on MRI and affects the surrounding tissue. This can lead to permanent deficits, depending on location. Recent studies, based on the analysis of MRI data, in which were included asymptomatic patients as well, showed that the extralesional hemorrhage is very rare, with an average of 1% per patient in a year. (7)

Both intralesional and extralesional hemorrhages usually manifest with an acute onset of the headache, followed by focal neurological deficits or comitial crises. (7)

In a recent study is mentioned that the rate of bleeding in family-form cavernomas is also influenced by the type of genetic mutation present. Carriers of the CCM3 genes, especially the younger patients, are more predisposed to intracerebral bleeding than carriers of the CCM2 and CCM1 genes. (21)

Considering the location, infratentorial lesions, especially those of the brainstem, have a bleeding rate between 2,46-5% per patient-year, higher than that of supratentorial lesions. However, the mechanism that increases the risk of bleeding in infratentorial lesions is not yet known. (22), (23)

Other symptoms:(18)

- Involuntary choreic movements caused by cavernomas located at the basal nuclei
- Cavernous sinus syndrome that may appear due to the presence of a cavernous sinus cavernoma
- Dementia and cerebellar signs appear in 70 years old patients in very few cases, so it is difficult to say whether the symptoms are due to lesion or age. (24), (25)
- Dystonia is a rare symptom associated with intracranial cavernomas
- Various types of visual deficits (26), (27)

3. Neuroimaging

- **CT scan examination**

On CT scan examinations, cavernomas appear as a hyperdense area to the adjacent parenchyma (due to impregnation with hemosiderin), inhomogeneous, round or irregular, well delimited, sometimes with calcifications (40-60% of cases) and usually without edema. After the administration of contrast substance, each cavernoma can be seen differently. (2), (7), (18)

Due to the low blood flow in the nidus, the lesion can be negative on angio-CT, except for larger lesions. (7)

- **Digital subtraction angiography (DSA)**

Although cavernomas are classified as angiographic occult lesions, digital subtraction angiography is negative for only 30-40% of cases.[2] Occasionally, in the later phase of angiography investigation, a vascular blush can be observed. In the early phase, over 20% of intracranial cavernomas can reveal a vascular blush and the presence of drainage veins. (18)

Although angiography is not usually used to diagnose cavernormas, it can be performed to offer a differential diagnosis with other vascular cerebral malformations. Angiography reveals the exact pattern of the venous drainage from the surface of the brain, so it can be useful for planning the surgical approach. (17), (18), (19)

- **MRI investigation**

This method is the most sensitive in detecting cavernomas, allowing a reliable diagnosis in both asymptomatic cases or in cases with acute neurological deficits. Thereby, the number of identified cavernomas increased considerably and epidemiological studies based on MRI investigations were performed. (14), (28)

The typical image of a cavernoma on MRI includes a well-delimited, spherical, inhomogeneous lesion, with mixed hyper and hypointense areas, surrounded by a hypodense ring. Due to this mixed aspect, the lesion has been described by some authors as having the appearance of „popcorn", „salt and pepper" or „honeycomb". On flair sequences, the perifocal edema is identified, especially in acute lesions. Multiple melanoma and hemorrhagic metastases can be a possible differential diagnosis. (2), (7), (18)

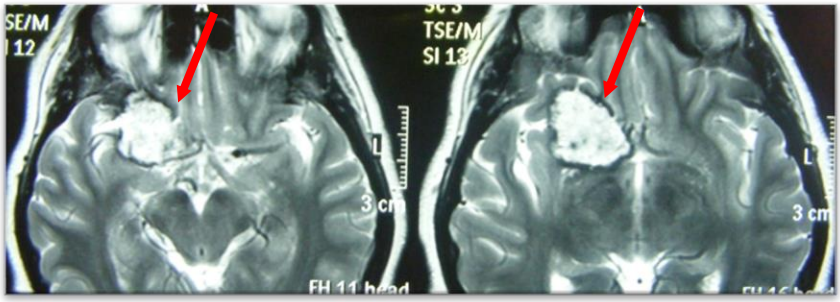

Figure 2. Axial MRI: Right fronto-temporo-insular cavernoma (Personal collection Prof. Dr. AV Ciurea)

Zabramski and colab. (1994) realized a classification of cavernomas based on the MRI view of the lesion. This classification has both diagnostic and prognostic value. The authors divide cavernomas into 4 categories (Table 1) (29).

Table I. Zabramski and colab (1994). classification of cavernomas (29)

Lesion type	MRI characteristics	Anatomopathological characteristics
Type I	T1: hyperintense nidus T2: hyper/hypointense nidus with hypointense margins	Subacute hemorrhage with a ring of macrophages impregnated with hemosiderin and gliotic tissue
Type II	T1: reticulated nidus with mixed signal T2: reticulated nidus with mixed signal and hypointense margins	Hemorrhage and thrombosis of varied ages; calcifications can be observed in large lesions
Type III	T1: iso/hypointense lesion T2: hypointense lesion with hypointense margins that	Chronic hemorrhage with hemosiderin staining in and around the lesion

Lesion type	MRI characteristics	Anatomopathological characteristics
	magnifies the size of the lesion GRE: similar to T2, but with greater magnification	
Type IV	T1: not visible T2: not visible GRE: punctate hypointense lesion	Small cavernoma with telangiectasia

Functional MRI investigation combines both anatomical and functional information. It is useful in preoperative planning for expansive processes that affect eloquent brain areas. This MRI function does not allow the visualization of the nerve fibers path, so functional MRI must be combined with DTI (Diffusion Tensor Imaging). All this data is necessary for neuronavigation.

4. The management of intracranial cavernomas

There is no standard treatment that can be applied to all patients with intracranial cavernomas. Most of the cavernoams are neurovascular lesions that do not endanger the patient's life and rarely produce permanent disabilities. However, some patients have a high risk to develop permanent sequelae due to bleeding or chronic epilepsy.

There are 4 therapeutic options for intracranial cavernomas: (2)

- Clinical and imaging monitoring
- Medical treatment
- Surgical resection
- Stereotactic radiosurgery

Ciurea et al. (2011) offer an algorithm for the therapeutic decision based on symptomatology, location of the lesion and genetic data. (2)

Table II: Algorithm for therapeutic decision according to Ciurea et al. (2011)

Symptoms	Location	Treatment
Asymptomatic	Indifferent	Yearly follow-up based on clinical and paraclinical criteria (MRI)
Severe headache, seizure, progressive neurological deficit	Non-eloquent areas	Surgical resection In case of incomplete resection, reintervention is recommended.
Drug resistant seizures, repeated or severe bleeding, progressive neurological deficits	Eloquent and/or deep areas	In case of incomplete resection, reintervention will be analyzed from case to case.
Epileptic seizures	Supratentorial	It depends on the severity of the crises, on the lesion`s location and if it is drug resistant.
Epileptic seizures	Multiple lesions	Paraclinical investigations (EEG, ECC) to determine which lesion is epileptogenic. If the lesion is accessible and it is not in a eloquent area, fast surgical resection is recommended.

Symptoms	Location	Treatment
Symptomatic or asymptomatic	Multiple lesions (familial form)	Genetic screening is recommended for the entire family.
Symptomatic	Non-eloquent area	In case of incomplete resection, surgical reintervention is recommended.

Conservative therapy

Clinical and imaging monitoring

Regardless of the lesion`s location, the elective management for asymptomatic patients is the conservative therapy. The patients should be observed clinically, and neuroimaging investigations should be performed once a year. The surgery should be performed in case the patient's condition deteriorates and/or the lesion increases in size. (2)

The management is different in case of multiple lesions. The surgical approach is reserved for superficial or accessible lesions, or when the patient has severe symptoms. In the familial form of cavernomas, a clinical and imaging monitoring of all family members must be performed. (2)

The presence of comitial seizures needs further investigations in order to identify the epileptic loci. The surgery will be recommended only when the lesions are responsible for drug-resistant seizures. (18)

Medical treatment

The medical treatment for supratentorial cavernomas is only symptomatic and consists of analgesics for headache and antiepileptics for the control of seizures. The antiepileptic therapy can continue after the resection of the cavernoma, until clinical or paraclinical changes (MRI and EEG). (30)

Surgical treatment

The treatment for most cases of cavernomas is surgery, due to their easy approach and due to their adjacent yellow gliotic tissue which separates them from the rest of the brain tissue. However, this does not apply for asymptomatic cavernomas or for the ones discovered incidentally. In general, surgical treatment is recommended for

symptomatic cavernomas with neurological deficits, comitial seizures or important bleeding. (2)

The aim of the surgical treatment is the complete resection of the lesion, together with the adjacent gliotic tissue. Same as in AVM, a subtotal resection can increase the risk of an intraparenchymal hemorrhage. In case of a lesion located in an eloquent area of the central nervous system, any rough handling of the tissue can determine ischemic or mechanic sequelae with disfunctions of the damaged centers. (2)

A preoperative planning is required, using all the neuroimaging investigations available (MRI „gold standard", functional MRI, angio-MRI and DTI) to map all the critical areas adjacent to the lesion. This stage of the surgical intervention is very consequential, because even a small error in the surgical approach can lead to difficulties to identify a small lesion such as a cavernoma in the brain parenchyma. (7)

It is important to underline that a surgical plan that seems perfect does not always guarantee a success. The neurosurgeon may not find the lesion. After the craniotomy and after the intraoperative loss of some cerebrospinal fluid (CSF), the position of the brain can change and the accuracy of the neuronavigation decreases. (7)

Surgical treatment of brainstem cavernomas is one of the biggest neurosurgical challenges, requiring deep knowledge of functional neuroanatomy of the region and a remarkable dexterity. The decision to perform surgery is mainly based on the number of hemorrhages present, the neurological status and the precise location of the lesion in relation to the 4th ventricle or with CSF cisterns (267). Crossing even a tiny portion of healthy tissue on the way to the lesion can lead to devastating sequelae. (31)

Stereotactic radiosurgery

Stereotactic radiosurgery is recommended for patients with lesions located in the brainstem, basal ganglia or in the eloquent areas of the cortex. Due to its minimally invasive nature and to its short hospitalization, this method can be performed on patients of any age regardless of the general condition or comorbidities. (32)

Despite all this advantages, the long-term effectiveness of stereotactic radiosurgery is controversial. An irradiated cavernoma remains in the brain and compared to other vascular malformation, such as AVMs, the effect of stereotactic radiosurgery on intraluminal blood flow cannot be objectively quantified based on reliable radiological investigations. In addition, the morbidity rate varies between 2.5% and 59%, and the mortality rate between 0% and 8,3%. The complications of stereotactic radiosurgery include edema, necrosis, increased frequency of comitial seizures and recurrent hemorrhage. Higher dosimetry is obviously associated with an even higher risk of complications. (33), (34), (35)

Abbreviations:
AVM-Arteriovenous malformations; **DVA**-Development venous anomaly; **DSA**-Digital subtraction angiography; **DTI**-Diffusion Tensor Imaging; **CSF**-Cerebrospinal fluid; **CT**-Computer Tomography; **MRI**-Magnetic Resonance Imaging

Disclaimer: the authors declare no conflict of interests.

Refferences:

1. McCormick WF. The pathology of vascular ("arteriovenous") malformations. Journal of neurosurgery. 1966;24(4):807-816.
2. Florian IS, Abrudan C, Horaţiu I. Cavernoamele Cerebrale in Ciurea AV. (Coord), Tratat de Neurochirurgie, Vol. 2. Editura Medicala; 2011; 159-170
3. Koubeissi M, Alshekhlee A, Mehndiratta P. Seizures in Cerebrovascular Disorders: A Clinical Guide. Springer; 2015.
4. Bremer B, Carson N. A case of brain tumor (angioma cavernosum), causing spastic paralysis and attacks of tonic spasms. operation. Am J Med Sci. 1890;100:219-241.
5. Dandy WE. Venous Abnormalities and Angiomas of the Brain. Archives of Surgery. 1928;17(5):715.
6.Krayenbuhl H, Yaşargil M. Die Vaskulären Erkrankungen Im Gebiet Der Arteria Vertebralis Und Arteriabasilaris. Thieme-Verlag; 1957.
7. Kivelev J. Brain and Spinal Cavernomas – Helsinki Experience. PhD Thesis. Institute of Clinical Medicine, Faculty of Medicine, Helsinki: University of Helsinki; 2010

8. Uluç K, Kujoth GC, Başkaya MK. Operating microscopes: Past, present, and future. Neurosurgical Focus. 2009;27(3):E4.
9. Voigt K, Yaşargil M. Cerebral cavernous haemangiomas or cavernomas. Incidence, pathology, localization,diagnosis, clinical features and treatment. Review of the literature and report of an unusual case. Neurochirurgia (Stuttg). 1976;19:59-68.
10. Kivelev J, Niemelä M, Hernesniemi J. Treatment strategies in cavernomas of the brain and spine. Journal of Clinical Neuroscience. 2012;19(4):491-497.
11. Choquet H, Pawlikowska L, Lawton MT, Kim H. Genetics of cerebral cavernous malformations: Current status and future prospects. Journal of Neurosurgical Sciences. 2015;59(3):211-220.
12. Ohba S, Shimizu K, Shibao S, Nakagawa T, Murakami H. Cystic cavernous angiomas. Neurosurgical Review. 2010;33(4):395-400.
13. Sasaran A. Dificultati Clinico-Terapeutice in Cavernoamele Supratentoriale. Teza de doctorat. Universitatea de Medicina si Farmacie „Carol Davila", 2015.
14. Robinson JR, Awad IA, Little JR. Natural history of the cavernous angioma. In: Journal of Neurosurgery. Vol 75. Journal of Neurosurgery Publishing Group; 1991:709-714.
15. Barker FG, Amin-Hanjani S, Butler WE, et al. Temporal clustering of hemorrhages from untreated cavernous malformations of the central nervous system. Neurosurgery. 2001;49(1):15-25.
16. de Souza JM, Domingues RC, Cruz LCH, Domingues FS, Iasbeck T, Gasparetto EL. Susceptibility-weighted imaging for the evaluation of patients with familial cerebral cavernous malformations: A comparison with T2-weighted fast spin-echo and gradient-echo sequences. American Journal of Neuroradiology. 2008;29(1):154-158.
17. Bertalanffy H, Benes L, Miyazawa T, Alberti O, Siegel AM, Sure U. Cerebral cavernomas in the adult. Review of the literature and analysis of 72 surgically treated patients. Neurosurgical Review. 2002;25(1-2):1-53.
18. Ciurea AV, Coman TC, Gambardella G. Actualitati in Cavernoamele Intracraniene. Editura Universitara "Carol Davila"; 2005.
19. Ryvlin P, Mauguière F, Sindou M, Froment JC, Cinotti L. Interictal cerebral metabolism and epilepsy in cavernous angiomas. Brain. 1995;118(3):677-687.

20. Awad I, Jabbour P. Cerebral cavernous malformations and epilepsy. Neurosurgical focus. 2006;21(1).
21. Denier C, Labauge P, Bergametti F, et al. Genotype-phenotype correlations in cerebral cavernous malformations patients. Annals of Neurology. 2006;60(5):550-556.
22. Kudo T, Ueki S, Kobayashi H, Torigoe H, Tadokoro M. Experience with the Ultrasonic Surgical Aspirator in a Cavernous Hemangioma of the Cavernous Sinus. Neurosurgery. 1989;24(4):628-631.
23. Kondziolka D, Lunsford LD, Kestle JRW. The natural history of cerebral cavernous malformations. Journal of Neurosurgery. 1995;83(5):820-824.
24. Kageyama Y, Kodama Y, Yamamoto S, Tadano M, Ichikawa K. A case of multiple intracranial cavernous angiomas presented with dementia and parkinsonism--clinical and MRI study for 10 years. Rinsho Shinkeigaku. 2000;40(11):1105-1109.
25. Ohara K, Shinjo T, Nishii R, Takeda K, Kokai M, Morita Y. [A case of intra-axial multiple cavernous angiomas, presented with dementia and cerebellar signs]. Seishin shinkeigaku zasshi = Psychiatria et neurologia Japonica. 2002;104(7):585-594.
26. Elmaci I, Ates G, Kurtkaya O, Pamir N. Chiasmal cavernous malformation. A rare cause of acute visual loss. J Neurosurg Sci. 2000;44(4):226-229.
27. Mejico LJ, Bergloeff J, Miller NR. Peripheral homonymous scotomas from a cavernous angioma affecting fibers subserving the intermediate region of the striate cortex. American Journal of Ophthalmology. 2001;132(3):440-443.
28. del Curling O, Kelly DL, Elster AD, Craven TE. An analysis of the natural history of cavernous angiomas. Journal of Neurosurgery. 1991;75(5):702-708.
29. Zabramski JM, Wascher TM, Spetzler RF, et al. The natural history of familial cavernous malformations: Results of an ongoing study. Journal of Neurosurgery. 1994;80(3):422-432.
30. Bremmer L, Carson N. A case of brain tumor (angioma cavernosum) causing spastic paralysis and attacks oftonic spasms: Operation. Am J Med Sci. 1890;100:219-242.
31. Samii M, Eghbal R, Carvalho GA, Matthies C. Surgical management of brainstem cavernomas. Journal of Neurosurgery. 2001;95(5):825-832.

32. Kondziolka D, Lunsford LD, Flickinger JC, Kestle JRW. Reduction of hemorrhage risk after stereotactic radiosurgery for cavernous malformations. Journal of Neurosurgery. 1995;83(5):825-831.
33. Pham M, Gross BA, Bendok BR, Awad IA, Batjer HH. Radiosurgery for angiographically occult vascular malformations. Neurosurgical focus. 2009;26(5).
34. Hsu PW, Chang CN, Tseng CK, et al. Treatment of epileptogenic cavernomas: Surgery versus radiosurgery. Cerebrovascular Diseases. 2007;24(1):116-120.
35. Alexander E 3rd, Loeffler J. Radiosurgery for intracranial vascular malformations: techniques, results, and complications. Clinical neurosurgery. 1992;39:273-291.

ARTERIOVENOUS MALFORMATIONS

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Homines dum docent discunt
Seneca, Ad Lucilium epistolae, Epistole morale

Contents

1. Definition

Intracranial arterial-venous malformations (AVM) are complex vascular abnormalities of a congenital nature that consist of a complex network of arterial-venous fistulas without the interposition of a capillary bed between the arterial source and venous drainage. The absence of the capillary bed leads to ischemia of the brain in the central area of the malformation (nest) and to the appearance of characteristic symptoms. Moreover, the rupture of the malformation has a major vital risk and that is why this pathology has a major indication for microsurgical treatment.

2. Differential diagnosis

The differential diagnosis is made based on the symptoms of subarachnoid or intracerebral hemorrhage, based on epileptic seizures (specific for cortical AVM) and based on slow progressive motor deficits (due to ischemic damage to the brain parenchyma). The differential diagnosis is made with:

- Cerebral amyloid angiopathy
- Stroke variant
- Cerebral aneurysms
- Cerebral venous thrombosis
- Migraine
- Intracranial expansive processes
- Moya Moya disease
- Galen vein malformation
- Venous angiomas.

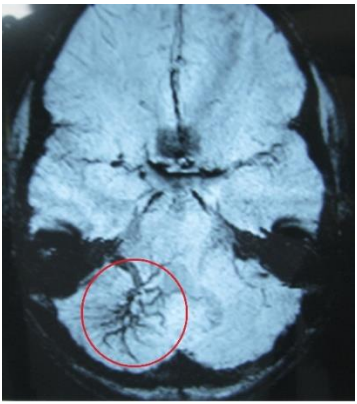

Figure 1. Typical aspect of "caput medusa" in a venous angioma. (Personal case of Prof. AV Ciurea MD.)

3. Incidence

Arteriovenous malformations have a frequency of approximately 15 cases / 10,000 individuals, regardless of sex and represent 6% of brain damage. Family incidence has rarely been described (11).

Regarding the major risks of a patient with AVM, data from the literature (12) show that they include:

- Unbroken AVM bleeding rate of 3-4% per year,
- In deep locations (midbrain, basal nucleus, brainstem) the bleeding rate is 60% per year (1% of patients die annually),
- The death rate in AVM is 1-2% per year and is associated with:
  - 10% with the first bleeding,
  - 13% with the second hemorrhage,
  - 20% with the following hemorrhages.
- The cumulative bleeding of AVM is 33% in 4 years:
  - 30% of survivors have morbidity: neurological deficits and / or epilepsy,
  - 7.6% of patients with AVM develop an aneurysm over time.

All AVMs have a pronounced tendency to increase in size and volume, therefore treatment should be instituted at the first clinical manifestation in decades 2 and 3 of life [6].

The essential elements of an AVM are:

- volume of arterio-venous malformation,
- superficial or deep localization of AVM,
- associated vascular abnormalities,
- the presence of bleeding (8).

4. Morphology

90% of AVM's have a supratentorial location. Most of the arterial feeders come from the medial cerebral artery, anterior cerebral artery and posterior cerebral artery. When they are first discovered, 30% of AVM's have a size just under 3 cm, 60% have a size between 3-6 cm and the remaining ones are above 6 cm.

As stated above, AVM's are composed of vessels with a different caliber, but without interposing capillaries. The vessels present multiple changes, such as calcifications, which increases the chance of them suffering a rupture. The surrounding cerebral structures suffer gliosis, therefore the risk of suffering epileptic seizures is increased.

5. Clinical symptoms

According to 'Adams (1993)' the initial symptoms, in order of frequency, are:

- cerebral hemorraghe
- epileptic seizures
- intense headache
- a progressive neurologic deficit
- while 15% of patients who are diagnosed with an AVM are asymptomatic.

Most frequently, AVM's are discovered in the 3rd decade of life. The symptoms described can be explained as follows:

- cerebral hemorrhage is the main clue and must be investigated thoroughly, considering that the cause can be a ruptured AVM. The risk factors that can rupture an AVM can cause a bleeding are: physical straining, stress, hypertension episodes, cranio-cerebral trauma, pregnancy, alcohol abuse, drugs, etc.

- epileptic seizures is the second symptom with regards to frequency; the cause is most often the cerebral gliosis of the surrounding cerebral parenchima or the cerebral ischemia.
- the 'pseudo-tumoral; syndrome of an AVM can be found in massive AVM's which are located in the posterior cerebral fossae.
- the progressive neurological deficit is found in 21% of all cases and happens because of the cerebral ischemia.

6. Investigations

Most often, the first investigation is a CT-scan, but it usually needs a more thorough examination, which if represented by an MRI or a cerebral angiography (it offers a more cleared image of the arterial feeders, size of the nidus, and the venous drainage).

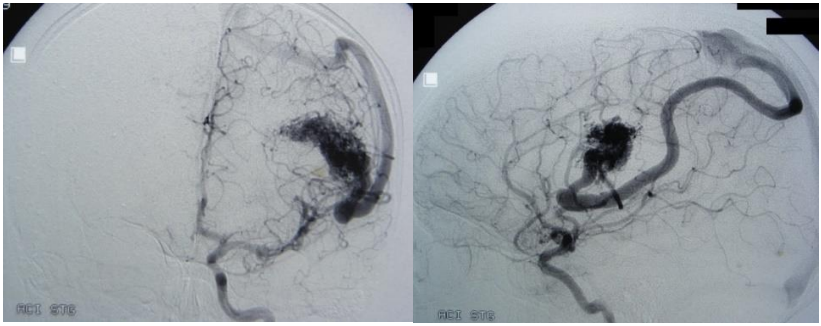

Figure 2. Grade II arterial venous malformation in 13-year-old children. (Personal case of Prof. AV Ciurea MD.)

7. Angiographic classification of MAVs

Table 1. Martin-Spetzler Classification – 1986

MAV	POINTS
< 3 cm – small MAV	1
3 - 6 cm – medium MAV	2
> 6 cm – large MAV	3
ELOQUENCE	

Non-eloquent	0
Eloquent	1
VENOUS DRAINAGE	
Superficial	0
Profound	1

AVM's are graded utilizing the scale proposed and made famous by Martin and Spetzler (1996). According to this scale, the severity of a lesion has 6 grades, with I being the lowest and VI the highest. Grades I through III have a high chance of a successful surgery outcome, while grades IV-V have a high chance of a permanent neurological deficit. At a later time, grade VI on the Martin-Spetzler scale has been added, and represents the inoperable AVM's.

8. Treatment

Modern treatment options are:

- classic surgery
- Gamma Knife stereotactic surgery
- endovascular treatment
- combinations of the above

The purpose of treatment is to stop the bleeding, to remove the AVM and to reduce as much as possible the neurological deficit. Each treatment is adjusted to each patient:

- small AVM's without profound venous drainage and that are situated in non-eloquent areas are usually treated with "open microneurosurgery"
- radiosurgery is preferred when the AVM is profound, with a diameter smaller than 3 cm, have a history of bleeding, in older patients.
- the goal of endovascular treatment is to remove the arterial feeders and to diminish the risk of bleeding. As a result, the AVM gets progressively smaller and it facilitates surgical removal.

As a rule, micro-neurosurgery cannot remove a profound AVM without leaving the patient with long-lasting or permanent neurological deficits. Stereotactic radiosurgery may present complications when used to treat AVM's that are bigger than 3 cm in

diameter. Last but not least, endovascular treatment represents a 'cure' only in 5-10% of cases, but is usually used before classic surgery then treating massive AVM's. Endovascular treatment can also preceed radiosurgery, can also treat associated aneurysms or arteriovenous fistulas in plexiform AVM's.

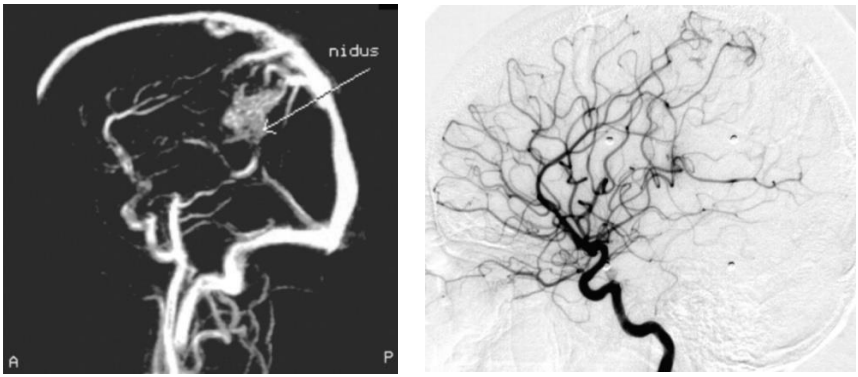

Figure 3. Pre and post-operative angiography in a grade III AVM. (Personal case of Prof. AV Ciurea MD.)

8.1. Surgical treatment

Surgical treatment of an AVM can be done only in specialized centers, with adequated technical capabilities si that can assure competent investigations, best intraoperative conditions, good care and postoperative treatment.

The surgery is made under general anesthesia and complete intraoperative monitorization. It is made using a large craniotomy and a carefully opening of the dura mater without damaging the superficial/cortical areas of said lesion. With regards to the profound or central located lesions, it is almost always imperative to use intraoperative neurophysiologic monitoring and more often than not repeat an intraoperative angiography as many times as necessary.

9. Complications

The intraoperative complications and risks are many, the most frequent one being intracerebral hemorrhage at the site of nidus

removal. In case of a faulty clipping of the drainage veins, before removing the arterial feeders, the AVM gets suddenly bigger in volume and has a high chance of bleeding.

The postoperative microneurosurgical complications are represented by hematomas at the former AVM position, edema and hemorrhaging by going over the normal cerebral perfusion pressure which leads to retrograde venous occlusions or cerebral vasospasm. In 7 to 15% of cases, 'de novo' seizure may appear.

10. Gamma Knife surgery

The method is represented by irradiation using a beam made of 201 convergent Gamma sources, which is directed at the AVM, in one sitting.

The purpose of radiosurgery is to completely remove the AVM when the volume of the nidus is between 5-10 cm3. Complete obliteration has a 1-to-3-year latency after radiosurgery in 80-85% of cases, but during this time the patients is exposed to sudden bleedings, hence bleeding being the most common complication.

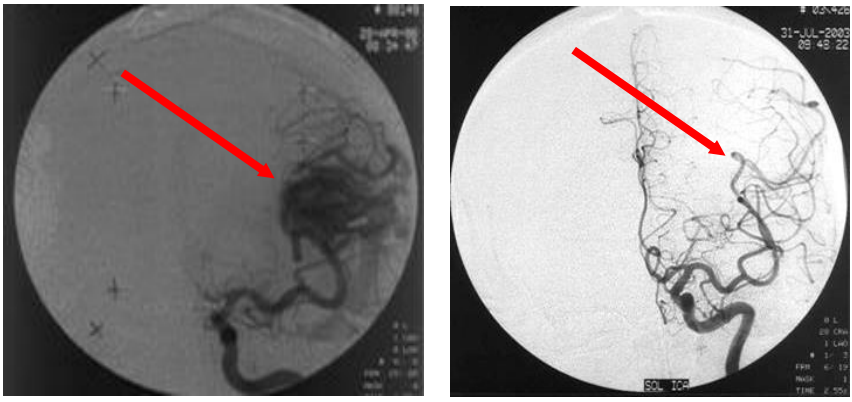

Figure 4. Angiography of pre (left) and post (right) Gamma Knife Surgery of a left temporal AVM
(Personal case of Prof. Dr. AV Ciurea.)

11. AVM Embolization

The purpose of embolization is to permanently reduce the size of the AVM and the blood flux, significantly reducing the chance of secondary bleedings and offering a safer and easier surgery or Gamma Knife treatment of the AVM. Nowadays, the material used in embolization are removable Gugliemi spires and organic cements. Final results and following complications depend on how well equipped the center is and, of course, in case selections. Intraoperative embolization has a higher precision and can save important vascular areas. As usual, the highest risk is intracerebral hemorrhaging.

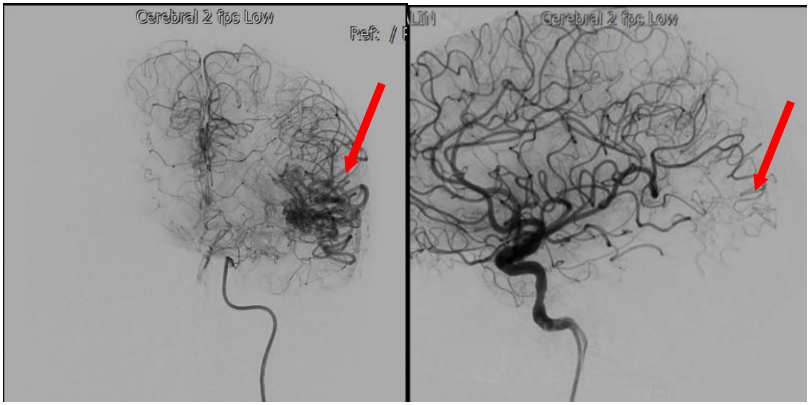

Figure 5. Angiography of pre (left) and postoperative (right) embolization using Onyx 18 of a left parieto-occipital AVM
(Personal case of Dr. C Mihalea and Prof. Dr. AV Ciurea)

12. Prognostic

Follow-ups are made doing each day a full neurological exam and an angiographic examination at 7 days post-treatment. Surgery exclusion rate is almost 98% of operated cases. Neurological degradation is below 5% in AVM's under 3 cm and 10-25% in medium AVM's (3-6cm).

In grades I, II, III AVM's, the mortality rate is estimated around 5.7%, while in grades V and VI it's about 30%. Morbidity in grades I, II and III is 4.8% and 65% in grades V and VI.

All literature data considers that grade VI AVM's are above treatment, and all it can be done is giving antiepileptic and conservatory treatment. In some cases, it can be chanced a partial embolization.

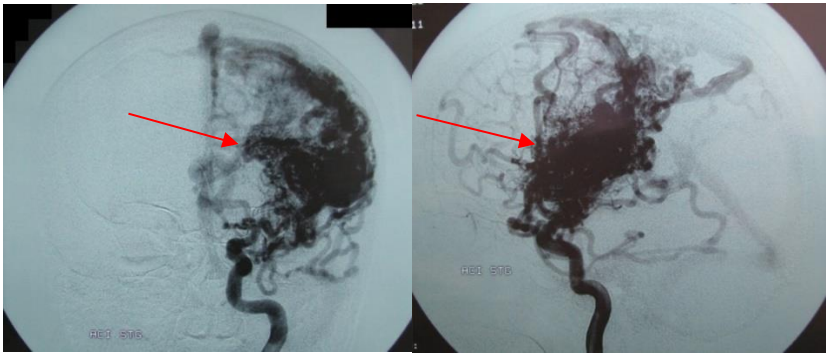

Figure 6. Grade IV AVM.
(Personal case of Prof. AV Ciurea MD.)

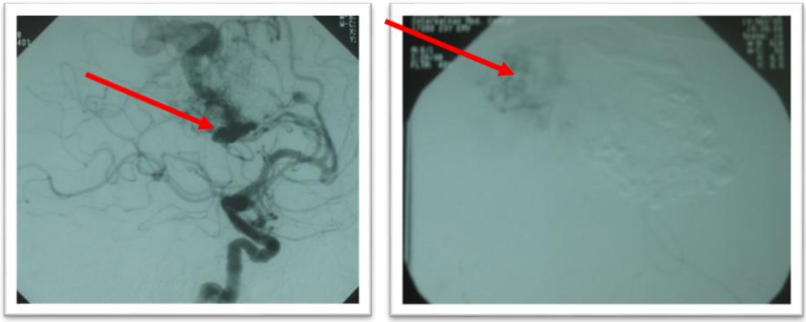

Figure 7. Left frontal AVM Grade IV – pre (left) and post embolization (right).
(Personal case of Prof A. Chefneux MD.)

Conclusions

Intracranial arterial-venous malformations (AVM) are complex vascular abnormalities which consist of a complex network of arterial-venous fistulas without the interposition of a capillary bed between the

arterial source and venous drainage. The absence of the capillary bed leads to ischemia of the brain in the central area of the malformation (nest). Superficial AVM often presents with associated epileptic seizures. Hence, any patient with epileptic seizures, progressive neurologic deficits and hemorrhagic stroke must be fully investigated for a possible AVM. Moreover, the rupture of the malformation has a major vital risk and that is why this pathology has a major indication for microsurgical treatment. AVMs grade I-III are best managed with surgery and/or gamma knife surgery. Microsurgical excision of AVM along with cerebral gliosis is the treatment of choice. Large AVMs (grade IV) in functional areas require a multimodal treatment – embolization, surgery and radiosurgery.

Abbreviations: AVM - arterio-venous malformation, **DSA** - Digital Substraction Angiography, **CT** - Computed Tomography, **MRI** - Magnetic Resonance Imaging.

Disclaimer: the authors declare no conflict of interests.

References:

1. Ausman J.I., et.al., Multidisciplinary approach to AVM, Operative Neurosurgery, Harcourt Publishers Limited, P 1137-1151, 2000.
2. Chapman P.H., et.al., Multimodality treatment of Nongalenic AVM in Pediatric Patient, Neurosurgery, 47, No 2,P 346-354, 2000.
3. Constantinovici Al., Ciurea A.V., Ghid practic de neurochirurgie, Editura Medicală, Bucureşti, 1998.
4. Ciurea A.V., Quality of life in intracranial AVMs, an experience of 224 cases, Congresul CENS (Central European Neurosurgical Society), Praga, 2012.
5. Ciurea A.V., Tratat de Neurochirurgie Vol. 1, Editura Medicală, București, 2010.
6. Ciurea A.V., Tratat de Neurochirurgie Vol. 2, Editura Medicală, București, 2011.
7. Gorgan R.M., Bucur N., Neacsu A., Difficulties in the treatment of cerebral arteriovenous malformations, Romanian Neurosurgery, Vol. XI, 2, 39-45, 2003.

8. Gorgan R.M., Bucur N., Neacsu A., Tratamentul multimodal al malformaţiilor arterio-venoase supratentoriale, Neurologia Medico-Chirurgicală, Timişoara, 2004.
9. Gorgan R.M., Bucur N., Neacsu A., Malformaţiile arterio-venoase supratentoriale, principii de tratament, Revista Româna de Stroke (AVC), Vol.VIII, NR.I, 2005.
10. Gorgan R.M., Malformaţiile arterio-venoase cerebrale, Tratat de Patologie Chirurgicală, sub Redacţia Prof.Dr. Irinel Popescu, Volumul Neurochirurgie, Editura Academiei, 2008.
11. Schramm J., Schaller C., Operative treatment of AVM's, EANS Course, Amsterdam, p19-21, 2001.
12. Spetzler R., Martin N.A., A proposed grading system for AVM's, J Neurosurg., 65:476-83, 1986.
13. Spetzler R., et.al., Supratentorial AVM, Operative Neurosurgery, Harcourt Publishers Limited, P 1080-1091, 2000.
14. Steiner L., Yen C.P., Jain S., Haq I.U., Jagannathan J., Schlesinger D., Sheehan J., Repeat γ knife surgery for incompletely obliterated cerebral arteriovenous malformations, Neurosurgery, 67: 55-64, 2010.
15. Chefneux A., Ciurea A.V., Tratamentul endovascular şi chirurgical al anevrismelor intracraniene, Editura Bennet, 2007.

INTRACRANIAL TUMORS – INTRODUCTION

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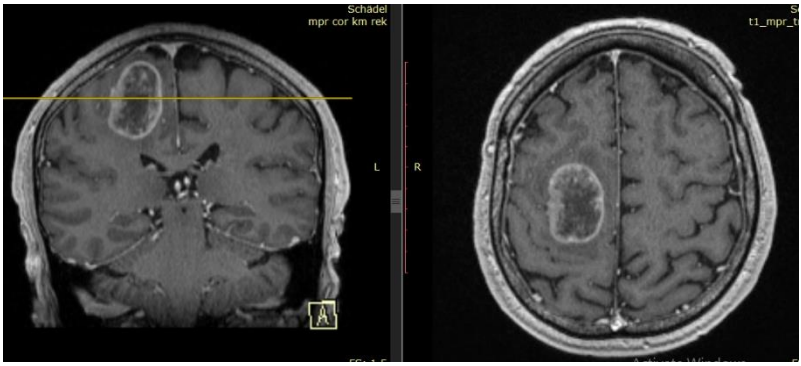
The work will teach you how to do it
Estonian Proverb



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Contents

1. Definition. Basics. Epidemiology

Brain tumours represent expansive intracranial processes clinically characterized by the appearance of ICP syndrome and a neurological location syndrome. ICP is given by the occurrence of the cerebral edema and the neurological location syndrome by the compression or the invasion accomplished by the tumour over the surrounding cerebral tissue.

Literature data shows that 2% out of all neoplastic lesions and intracranial (1). Statistics surrounding primary tumors as well as secondary (metastatic) tumors show that intracranial tumors (ICT) are responsible for about 8% of mortality dues to tumors (1). This is mainly due to life expectancy growth and to multiple metastatic tumors, mainly pulmonary, cutaneous, digestive and from the nervous central system.

When it comes to the intracranial site of the tumors, 2/3 are supratentorial, while 1/3 are infratentorial. Frontal tumors are the most often found tumors, followed by temporal and parietal ones. The next more common are intraventricular and then basal ganglia tumors. In adults supratentorial tumors are more common, while in children (0-16 years of age) infratentorial tumors are more frequent (70%). The is no age group that is mainly involved, with this pathology affecting individuals of any age (2).

Intracranial tumors are twice as frequent in male patients. In male patients more commonly found are medulloblastoamas, astrocytomas

(supra- and infratentorial), pinealoamas, while in female patients meningiomas, acoustic neuromas and pituitary tumors are more common (3).

Considering the histopathology of intracranial tumors gliomas of various types are predominant. Statistics show that around 50% of intracranial tumors in adults are gliomas, followed by decreasing frequency by meningiomas, metastasis and neuromas (3).

The importance of intracranial tumors is a major one, because these tumors develop into a limited, closed space (the skull) in which there is room for only 3 elements:

- Cerebral parenchyma
- CSF (major component)
- The blood component.

Any displacement in the equilibrium between these three elements that co-function perfectly together leads to major phenomena and to symptoms of expanding intracranial masses, which is often progressive and invalidating; progressive because of the continuous growth of the expanding mass and invalidating because of compression or infiltration of the neural structures in its proximity (4).

2. Complications of the expanding nature of intracranial tumors

Cerebral edema

Some types of meningiomas, malignant gliomas and especially metastasis are accompanied by a considerable reactive edema, to which mass effect of the tumor volume is added.

This perilesional edema is of vasogenic etiology. Edema liquid originates from the tumor, because of neoplastic capillaries develop structural gross anomalies. The increased capillary permeability that leads to edema formation also helps outflow of protein markers used as a contrast medium in neuro-imagery.

The volume of the edema depends on a hydrostatic equilibrium between the intravascular pressure that tends to get liquid out and tissular pressure that opposes the flow-out, a progressive resistance that increases as the edema enlarges. Moreover, in case of a slow growing tumor, absorption phenomena secondary occur: edema liquid drainage into the ventricles and re-absorption of flowed proteins from the

astrocytes. A permanent dynamic equilibrium is achieved between factors that promote the edema and factor that oppose it.

Peritumoral edema volume may vary depending on local aspects: pressure gradient generated by tumor growth, toxic phenomena generated by tissular necrosis or systemic disfunctions - variation of serum osmolarity, venous pressure and pCO_2.

Anatomically, edema develops within the white matter. The gray matter of the cerebral hemispheres, brainstem and cerebellum, where hydraulic resistance is higher, are not affected.

Tumoral hydrocephalus

The main part of tumoral hydrocephalus is of obstructive etiology and conditioned by the obstruction of CSF circulation within the lateral ventricles or more frequently within the 3rd and 4th ventricle.

Communicant hydrocephalus is rare and develops during neoplastic invasion of leptomeningeal tissue or because of significant hyperalbuminorachy that accompanies some intracranial or intraspinal tumors. Ventricular dilation can develop in a few hours beginning in the frontal horns and can later extend into the whole ventricular system. **2**

Anatomical and clinical expression of hydrocephalus depends on speed of the tumor growth, site of the tumor, and patient age. Hydrocephalus with typical and severe intracranial hypertension syndrome is found in children and young patients. In elderly patients with increased cerebral compliance, hydrocephalus often presents like a "normal pressure hydrocephalus" (NPH), with the dominance of gait disfunction and sphincter control disfunction.

Intracranial hypertension (ICH)

An intracranial tumor progresses often in weeks, months or even years. Phenomena of adaptation and compensation of the intracranial elements differ fundamentally from those that occur in the pathological event of an intracranial hematoma that progresses in minutes or hours. In intracranial tumors' pathology a rapid expansion is found only in particular situations: complete blockage of a hydrocephalus or intratumoral bleeding. Tumoral masses with a less acute development

or the ones that present with perilesional edema and hydrocephalus may determine global intracranial hypertension.

Most often the slow growth of the tumor allows for the brain parenchyma and the ventricular system to compensate, with intracranial hypertension occurring only in cases of end stage disease. Too conclude, the more acute the lesion, the earlier and the more severe the increased ICP phenomena occur, and the slower and longer the progression of the lesion, the more significant the local distortion and the later the increased ICP occurs.

Cerebral parenchyma dislocations

The presence of an intracranial tumor produces compression of the cerebral sulci, the cisterns and the ventricles. These structures collapse and then they are moved together with the vascular and nervous structures that cross through them. When a pressure gradient through a narrow opening develops (between the right and left hemispheres, the hemispheres and the posterior cerebral fossa, the posterior cerebral fossa and the spinal canal) some parenchymal structures can be pushed through these narrow openings, producing herniation phenomena:

The two major intracranial herniations are the following:

- *Temporal lobe uncus* herniation through the tentorial notch into the ambiens cistern and cerebral peduncle compression (transtentorial herniation). **Clinical correlation** – uncal herniation syndrome – contralateral limbs motor deficit, ipsilateral oculomotor nerve paresis, variable altered mental state
- *Cerebellar tonsillar* herniation (figure1), through the foramen magnum (in front of its bony margin) into the cisterna magna and compression of the bulbo-medullary junction.

Clinical correlation – tonsillar herniations syndrome - coma, Cushing reflex (Cushing's triad - bradycardia, arterial hypertension, cardiac arrythmias), hypoxemia

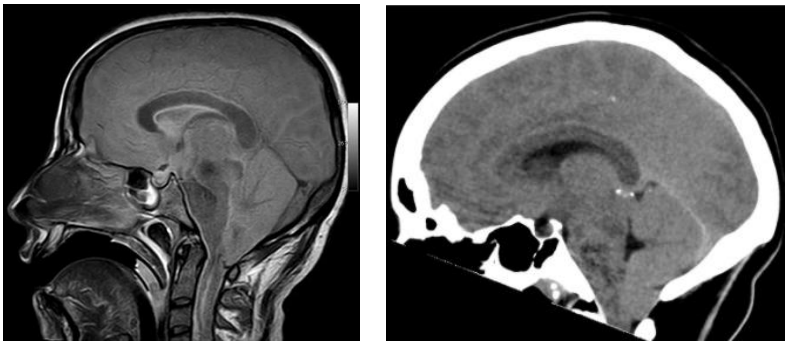

Figure 1. Tonsillar herniation.
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Other intracranial herniations:

- *Cingulate gyrus:* it herniates under the free margin of the falx in the pericallosal cistern (subfalcine herniation) (Figure 2).

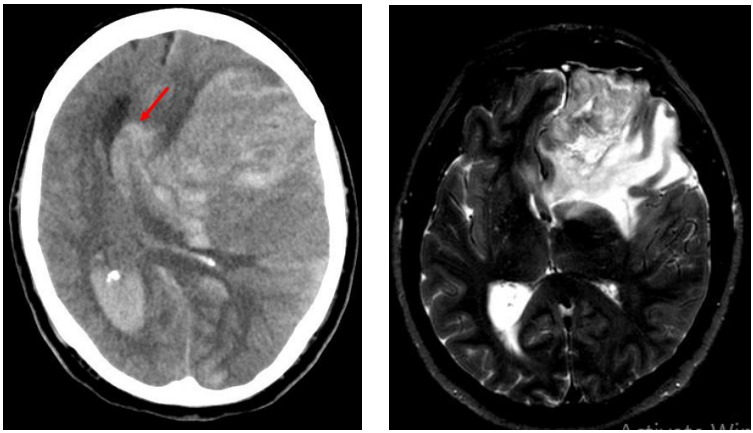

Figure 2. Sulfalcine herniation
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- *Cerebellar culmen* herniates into the quadrigeminal cistern, beyond the free margin of the falcotentorial junction and to the posterior aspect of the midbrain.

It is also possible for a tumor with proximal site during its growth to herniate itself through an opening: for example, the herniation of a medulloblastoma through the foramen magnum. Herniations are considered complication of increased ICP in the context of a push of the unaffected parenchymal by an expanding tumoral mass.

In lesions with a slow progression rate, significant cerebral substance dislocations may be found and even herniations such as the ones previously mentioned can occur by 'slipping', with disturbances in ICP.

The frequency of herniations among tumor conditions is difficult to estimate, but it is nonetheless very high because it is a common form of aggravation of end stage cerebral tumors.

3. Clinic data

Symptoms related to intracranial symptoms depend on the tumor's nature, benign or malignant, tumor's site, the number of tumoral lesions and patient's condition: age, sex, comorbidities etc. (5,6)

Symptoms due to increased intracranial pressure are as follows: headaches, psychiatric symptoms, emesis and papillary edema, accompanied by meningeal signs, cranial nerves palsy, vegetative disfunction and sometimes seizures.

Symptoms secondary to the lesion's site within the brain parenchyma are focal symptoms (irritations or/and deficits) and they form the clinical syndrome particular for each cerebral lesion.

Symptoms due to irritation consist of various types of seizure activity. Nonetheless generalized seizures with late onset or clinical variation of a preexistent epileptic syndrome need further neurosurgical examination.

Neurological focal symptoms are to be grouped into symptoms with following site:

- Cerebral hemispheres
- cerebellum
- brainstem.

These symptoms are variable as far as intensity goes with the evolutive stage of the lesion, patient's age and individual aspects. In children focal syndromes manifest quite lately, with the clinical

presentation at debut and even later on consisting mainly of intracranial hypertension phenomena. In adults focal neurological syndromes are much more obvious. (6)

4. Neurological syndromes

- **intracranial hypertension syndrome** – altered mental status (see below), headache, emesis, ocular pain
- **upper motor neuron syndrome** - motor deficits (paresis or plegia), especially slowly progressive ones; the motor deficit consists usually of monoparesis or hemiparesis, rarely paraparesis (in bilateral paracentral lobule lesions)
- **Babinski sign** – when it is unilateral it reveals s contralateral cerebral hemisphere lesion; the presence of this sign appears to be a reaction of 'freedom' from the control and influence of the inhibitory effect of the pyramidal tract
- **Bilateral Babinski sign** reveals the herniation of the cerebellar tonsils and is a neurosurgical emergency.
- **sensitive syndrome**: disfunctions of subjective sensitivity with deficits must be examined for superficial, thermic, tactile and pain sensitivity, as well as for the profound one. Sensitivity deficits reveal a parietal lesion.
- **speech disfunctions** – encountered in dominant cerebral hemisphere lesions, they are motor dysfunction (frontal lobe lesions – Broca aphasia) or sensitive disfunctions (parieto-temporal lesions – Wernicke aphasia)
- **praxia disfunction** is an important finding in parietal lesions and can be encountered in both dominant (constructive apraxia) and non-dominant (dressing apraxia) cerebral hemisphere lesions.
- **gnosis disfunctions** are revealing for lesions specific to cerebral lobes (visual – occipital lobe, tactile – parietal lobe)
- **visual field disfunctions** are specific for temporal lobe lesions (superior quadrantanopia), parietal lobe lesions (inferior quadrantanopia), occipital lobe lesions (homonymous hemianopia) and for optical pathway lesions

- **Space orientation disfunctions** are specific for frontal lobe pathology and also for its correlation with the parietal and occipital lobes
- **Cranial nerve palsy** is frequently found:
  - C.N. VI pair is affected in the increased ICP syndrome because of their trajectory through the base of the skull, resulting in convergent strabismus; nystagmus develops in posterior cerebral fossa tumors.
  - Oculomotor nerves dysfunction and disfunction of the latest pairs of cranial nerves are specific for brainstem tumors.
- **Trophic disfunctions** are encountered in supratentorial lesions: corpus collosum and parietal lesions.
- **vegetative disfunctions** can be found in temporal and fronto-orbital lesions
- **Extrapyramidal-like motor disfunctions** - hypertonia, rigidity, hypokinesia, in basal ganglia lesions.
- **Truncal ataxia** points to cerebellum involvement: vermian and nodulo-floccular lobuli involvement
- **Cerebellar syndromes (limb coordination disfunction)**, specific for cerebellar hemisphere lesions, present with *dysmetria, nystagmus, muscular hypotonia that causes pendular reflexes.*
- **Meningeal signs** point to a subarachnoid hemorrhage (possible ruptured arterial-venous malformations) or a posterior fossa tumor with herniation associated phenomena.
- **Psychiatric symptoms:** decrease of school performance, psychomotor regression, memory loss, attention disfunction, calculus, irritable status, agitation or apathy, indifference in regard to oneself, affectivity disfunction, character changes, critical sense loss and especially self-critical sense loss, gatism (loss of sphincter control, urinary and anal) can progress into the clinic of an intracranial tumor.
- **Neurological status alteration (of the consciousness status)** – from drowsiness and sleepiness, slight confusion with time and space disorientation, to obnubilation, stupor and coma, it is a common finding in deep tumors that affect the basal ganglia or any tumor, when they develop pressure cones that press on the midline structures.

5. Paraclinical diagnosis

Clinical examination should be conducted with great attention in order to catch every neurological sign that would eventually and gradually lead to major syndromes that suggests the site of the expanding intracranial lesion. Unfortunately, it is not rarely that the neurological examination is neglected, and neuroimaging tools are immediately done.

It should be noted that out of the complete human pathology the first capital element is patient history and the second the clinical examination. Depending on those the paraclinical examinations are conducted, justified by the facts presented above.

All the paraclinical imagery tools that are used lead to the gathering of aspects as complete as possible about the single of multiple intracranial lesions. Once the clinical diagnosis is made and the paraclinical aspects are gathered, mainly neuroimaging, can get a complete diagnosis can adopt an adequate and efficient therapeutic strategy, which can have an immediate effect(6,7)

Ophthalmological examination - its relevant components regarding the pathology in question include the eye fundus examination and visual field examination.

Examination of the eye fundus highlighting changes secondary to increased intracranial pressure and determination of the visual field may be altered in relation to some intracranial tumor locations. Examination of the eye fundus may reveal wiping of the papillary margins (stage I papillary edema) to post static optic atrophy (stage IV) or primitive optic atrophy.

Visual field examination focuses on the location of the lesion (see the visual field disorders described above).

Electroencephalography is of value in supratentorial tumors and can highlight an electric focus of *slow delta waves,* a cerebral hemisphere asymmetry, diffuse bioelectric changes.

EEG can be a useful test in exploring cranial tumors insofar as it indicates the lateralization of the injured hemisphere and even the focus of brain suffering. In posterior cranial fossa tumors, EEG reveals only bilateral diffuse bioelectrical changes (Figure 3).

Figure 3. Computerized EEG in a case of cerebral tumor (Personal collection of Prof. Dr. A. V. Ciurea)

Plain cranial radiography is of little informative value and is practically abandoned today. Rarely it may reveal bony deformities due to a close meningioma. (7)

Digital subtraction cerebral angiography (D.S.A.) methods and MRI angiography, Angio CT, allows highlighting the vascular pedicles of the lesion. Often, the DSA completely highlights the vascular pedicles and the venous distribution over the entire tumor area (venous blush from meningiomas).

Craniocerebral computed tomography (CT, CT-scan) has contributed fundamentally to the diagnosis in intracranial tumors. The major advantages of this investigation are due to the minimal invasiveness, the multiple informational data about the craniocerebral structures, the possibilities of dynamic follow-ups.

By getting a CT scan we can exactly appreciate the site, form, extension, number and sometimes even the nature of extending masses and their associated effects on the ventricular system. The advantage

consists in rapid performance, possibility of repeating in dynamics, the elements that can be obtained being the following:

- **indirect** signs of expansive process, represented by the displacement of the midline structures, choroidal plexus displacement, compression and deformation of the lateral ventricles, CSF blocking with consecutive hydrocephalus.

- **space replacement process.** Compared to the surrounding brain tissue, tumour intensity can be low (when it contains fat or fluid) or increased (when it contains calcification or bleeding, necrosis). Sometimes, tumours can have the same intensity as brain tissue, for differentiation, it is necessary to administer a contrast agent.

- **perifocal tumour edema** occurs in the white matter around the expansive process and has a low density compared to brain parenchyma (Figure 4).

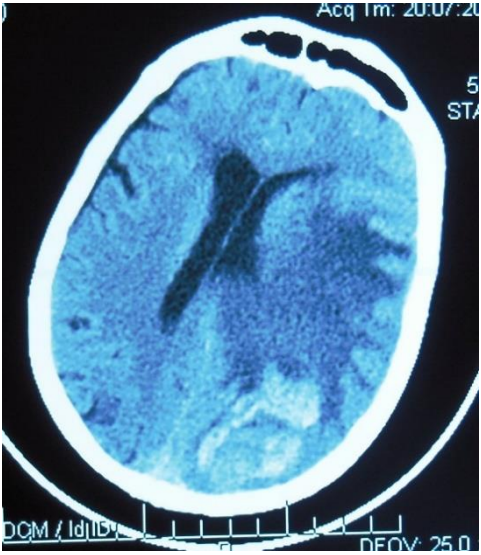

Figure 4. Peritumoral digitiform cerebral edema (Personal collection of dr. Vicențiu Săceleanu)

Contrast material administration can ease the process of revealing the tumor, which can appear hypodense, isodense or hyperdense can

have a mixed structure. Unfortunately, this major screening method gradually lost its accuracy, being overruled by the MRI and its multiple features. Moreover, MRI does not require any kind of irradiation of the body.

Magnetic resonance imaging (MRI) and its variants (plain and with contrast enhancement: perfusion MRI, diffusion MRI, functional, spectroscopy MRI, perfusion, de difuzie, funcţională, spectroscopică = magnetic resonance spectroscopy= SMRI) are getting as performant as can be. MRI complete and event replaces the CT scan, being very useful for detecting expanding masses located around the midline structures and the posterior cranial fossa and can be used in patients with allergies to contrast material or renal failure. (Figure 5)

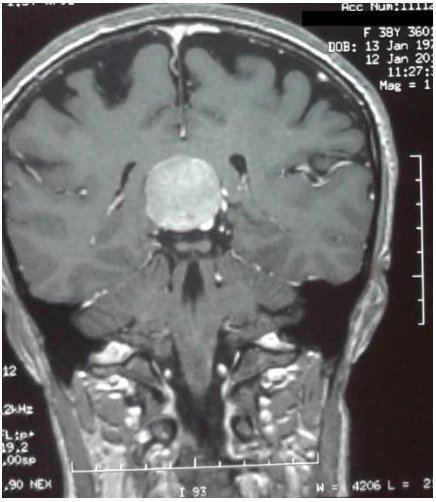

Figure 5. Contrast, enhanced MRI in a case of pineal region tumor – meningioma
(Personal collection of Prof. Dr. A. V. Ciurea)

There is also the MRI variant of angio-MRI (angiography by MRI) which appreciates the expanding mass and the vascular bundles.

Magnetic resonance imaging is very little used on comatose patients (due to lack of intensive care devices – exp.: MRI compatible ventilators).

The MRI is the “gold standard” imagery in all the expanding intracranial masses.

Positron emission tomography (PET) is used as a diagnostic tool to determine the grade of the tumor and can differentiate between tumor recurrence, radionecrosis lesion, and brain scarring. In principle, a low dose of 2-fluoro-2-deoxyglucose (FDG), which is radioactively labeled glucose, is used and brain metabolic activity is measured.

The main purpose of this investigation is to reveal the grade of tumor malignancy and / or the possibility of recurrence of the malignancy.

SPECT (Single photon emission computed tomography) uses a radioactive tracer, 99mTc-HMPAO (hexamethylpropylene amine oxime) which allows the study of brain metabolism. This investigation focuses on tumor recurrences and intracranial epileptogenic lesions.

6. Malignization process

The phenomenon of malignancy involves the appearance and excessive, disordered and irreversible development of a tissue mass, undifferentiated, dysfunctional and with progressive evolution. Malignancy occurs in several stages that constitute a "cascade of neoplastic change", this includes genetic change induced by various factors, tumor cell growth, angiogenesis, by neoformation vessels. Eventually invasion of the surrounding meningo-cerebral tissues occurs.

Malignancy can occur in tissues with pre-existing pathological changes: inflammatory, dystrophic, irritative, traumatic, etc. Pathological changes that do not regress may constitute "precancerous lesions." Precancerous lesions can turn into a certain percentage of intracranial tumors, due to general or local, exogenous or endogenous factors. They induce transformations in the genome of cells that affect essential cellular functions: control of cell division, maintenance of DNA integrity, apoptosis (1,6).

Malignancy occurs by activating an oncogenic gene or by inactivating an anti-oncogenic gene. These activated genes cause tumor phenotypic changes. The factors that cause the change in precancerous lesions into cancer are called "carcinogenic factors." Precancerous

lesions and carcinogens are often insufficient for the clinical manifestation of intracranial tumors. There are situations in which these latent lesions are discovered by chance by a brain scan (brain CT) performed for a reason other than the suspicion of a brain tumor (craniocerebral trauma, stroke, etc.).

Precancerous cerebral lesions

Many of these cerebral pathologies can become precancerous lesions [1]:

1. Embryonic precancerous lesions (remaining embryonic cells or with abnormal localization within some CNS regions that can progress to dysembrioplastic tumors etc.).
2. Desmoplastic glial proliferation: gliomatosis, microgliomatosis, tuberous sclerosis
3. Meningo-encephalitic inflammatory processes: some viruses can modify the genetic structure of infected cells as thus lead to the rise of a tumor.
4. Traumatic lesions. Traumatic brain injuries can provide precancerous cerebral lesions. This way the meningo-cerebral posttraumatic scar cand be the starting point for a tumor, through typical glial cells' division degeneration into atypical glial division. Glial posttraumatic proliferation can occur in proximity of the traumatic lesion but also in distant sites.
5. Radiation and chemical substances also have a role in precancerous lesions development because the metabolic distress they produce, especially within the glial and embryonal nervous tissue.

7. WHO classification of intracranial tumors

In 2016 the World heath Organization published an updated classification of intracranial tumors, in whose adaption aspects belonging to molecular biology where taken into consideration for the first time.

Neurosurgical practice is nowadays universally guided by this classification.

In 1925 Bailey and Cushing discovered that tumors that develop from differentiated cells have a slow evolution (years in oligodendrogliomas) and that tumors that develop from

undifferentiated or weekly differentiated cells (glioblastoma multiforme) are more aggressive, with a quicker progression and frequent postoperative recurrence.(3)

1. **Diffuse astrocytic and oligodendroglial tumors**
   - diffuse astrocytoma - IDH mutant/ IDH wildtype/ NOS
   - gemistocitic astrocytoma (IDH mutant)
   - anaplastic astrocytoma - IDH mutant/ IDH wildtype/ NOS
   - glioblastoma - IDH mutant/ IDH wildtype (giant cell glioblastoma, gliosarcoma or epithelioid cells glioblastoma)/ NOS
   - diffuse midline glioma - H3 K27M mutant
   - oligodendroglioma - IDH mutant/NOS
   - oligoastrocytoma – NOS
   - anaplastic oligoastrocytoma - NOS
2. **Other astrocytic tumors**
   - Pilocytic astrocytoma – with pilomixoid astrocytoma
   - pleomorphic xanthoastrocytoma
   - anaplastic pleomorphic xanthoastrocytoma
   - Giant cells subepedimal astrocythoma
3. **Ependimal tumors**
   - subependymomas
   - myxopapillary ependymoma
   - ependymomas – papillary, clear cells, tanycytic
   - ependymoma – RELA fusion positive
   - anaplastic ependymoma
4. **Other gliomas**
   - Choroid glioma of the 3rd ventricle
   - Angiocentric glioma
   - Astroblastoma
5. **Choroid plexus tumors**
   - Choroid plexus papilloma
   - Choroid plexus atypical papilloma
   - Choroid plexus carcinoma
6. **Neuronal and mixed neuronal-glial tumors**

Dysembryoplastic neuroepithelial tumor, gangliocytoma, ganglioglioma, anaplastic ganglioglioma, dysplastic cerebellar

gangliocytoma (Lhermitte – Duclos disease), infantile desmoplastic astrocytoma and ganglioglioma, papillary glioneural tumor, rosettes forming glioneural tumor, diffuse leptomeningeal glioneural tumor, central neurocytoma, extraventricular neurocythoma, cerebellar liponeurocytoma, paraganglioma

7. **Pineal region tumors**
   - pineocytoma
   - pineoblastoma
   - pineal tumor with intermediary differentiation
   - papillary tumor of the pineal region
8. **Embryonal tumors**
   - medulloblastomas
     - Genetically defined - WNT mutant, SHH mutant and TPS3 activated, SHH mutant and TPS3 wildtype, non WNT, non TPS3 (groups 3 and 4)
     - Histologically defined - clasical, desmoplastic/nodular, with extended nodularity, cu large cells/ anaplastic
   - medulloblastomas NOS
   - medullomyoblastomas
   - melanocytic medulloblastomas
   - multilayered rosettes embryonic tumor – NOS or altered C19MC
   - medulloepithelioma
   - CNS neuroblastoma
   - CNS ganglioneuroblastoma
   - CNS embryonic tumor – NOS
   - teratoid/rhabdoide atypical tumor
   - CNS embryonic tumor with rhabdoid features
9. **Cranial and paraspinal nerves tumors**
10. **Meningiomas** - meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, metaplastic, choroid, lymphoplasmocite rich, with clear cells, atypical, papillary, rhabdoid, anaplastic (malignant)
11. **Mesenchymal, non-meningothelial tumors**

Hemangiopericitoma (grades 1/2/3), hemangioblastoma, hemangioma, epithelioid hemangioendothelioma, angiosarcoma,

Ewing/PNET sarcoma, Kaposi sarcoma, lipoma, angiolipoma, hibernoma, myofibroblastoma, desmoid-type fibromatosis, mielofibroblastic, inflammatory mielofibroblastic tumor, benign fibrous histiocytoma, fibrosarcoma, leiomioma, malignant pleomorphic undifferentiated sarcoma/ fibrous histiocytoma, leiomiosarcom, rhabdomyoma, rhabdomyosarcoma, chondroma, condrosarcom, osteoma, osteochondroma, osteosarcoma

12. **Melanocytic tumors**
    – meningeal melanocytosis, meningeal melanocytoma, meningeal melanomatosis, meningeal melanoma
13. **Lymphomas**
14. **Histiocytic tumors**
    – Langerhans cells histiocytosis, Erdheim-Chester disease, Rosai-Dorfman disease, juvenile xanthogranuloma, histiocytic sarcoma
15. **Germ cells tumors**
    - germinoma, embryonic carcinoma, choriocarcinoma, Yolk sac tumor, teratoma (mature or imature), teratoma with malignant transformation, mixed germ cells tumor
16. **Tumors of the sellar region**
    - craniopharyngioma – adamantinomatous or papillary
    - granular cells tumor of the sellar region
    - spindle cells oncocytoma
    - pituicytoma
17. **Metastatis tumors**

For each of these subsets of tumors a grade (0/1/2/3) that correlates proportionately with the malignancy grade has been designated, so that grade 0 – benign, 1 – borderline or unknown, 2 – in situ carcinoma and grade III epithelial neoplasms and grade 3 – malignant.

Out of the older classifications we also continue to use, out of practical considerations, the division of glial cell tumors in low grade gliomas and high-grade gliomas. (12)

8. Treatment principles

The treatment is multimodal, addressing both the intracranial tumor itself and the side effects produced by the tumor on the brain structures:

- directly to the intracranial tumor:
  - surgical ablation of the tumor
  - stereotaxic or neuronavigated biopsy, with extemporaneous histopathological examination and further operation planning
  - radiotherapy
  - chemotherapy
- the effects of the tumor on the cerebral parenchyma (intracranial hypertension syndrome, seizures):
  - on cerebral edema - corticosteroid therapy, cerebral depletion (Mannitol, diuretics)
  - therapy for internal obstructive hydrocephalus - temporary external ventricular drainage, permanent ventricular-peritoneal drainage, endoscopic ventriculocisternostomy.

Surgical treatment of intracranial tumors

a) The treatment of intracranial tumors is mainly the surgical one and consists of *minimally invasive radical microsurgical resection.* The site of the intracranial tumors contributes very high to the type of surgical approach, complete tumor ablation being conditioned by the site of tumor. (16)

The surgical procedure has the following goals:

- total ablation;
- preservation of vasculo-nervous adjacent structures;
- reaching the histopathological diagnosis,
- decreasing the intracranial pressure by removing as much of the tumor as possible under safe conditions for the surrounding tissues, with insurance of CSF circulation,
- minimizing the compression on the surrounding brain parenchyma and amelioration of symptoms, diminishing the cerebral edema and decreasing the dose of anti-edema corticotherapy needed.
- Insertion of drugs into the tumor.

The surgical procedure should start with the following surgical desiderates which are mandatory:

- Total ablation of a part as great as possible of the tumor without damaging the vascular and nervous structures in its proximity
- CSF circulation pathway redoing.

Neurosurgical interventions currently benefit from important technological advantages, which have contributed to the reduction of surgical complications: microsurgery, intraoperative ultrasonography, ultrasonic aspiration, intraoperative scanning control (intraoperative MRI), neuronavigation and stereotaxis. Surgical treatment can be performed classically, by craniotomy, or endoscopically, depending on the location of the lesion. Modern neurosurgery data reveal an intraoperative mortality below 3%.

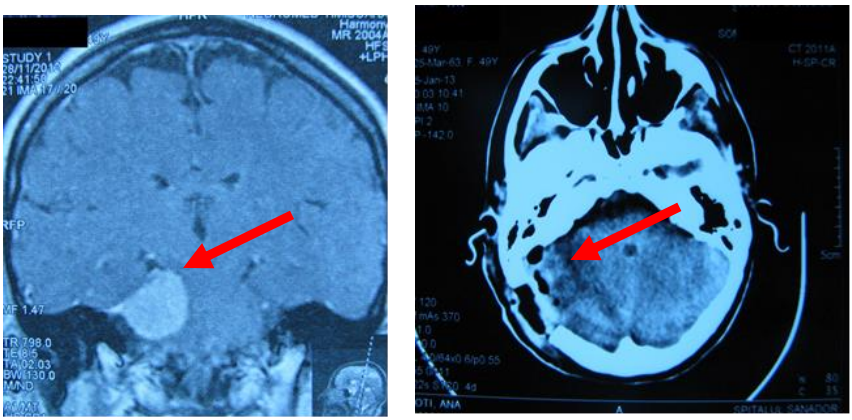

Figure 6. MRI aspects of petroclival meningioma pre- and postoperative (total ablation).
(Personal collection of Prof. Dr. A.V. Ciurea)

Posterior cerebral fossa tumors such as pilocytic astrocythoma are frequent in children and require a single treatment: complete surgical tumor resection, no radiotherapy or chemotherapy being necessary. (Figure 7).

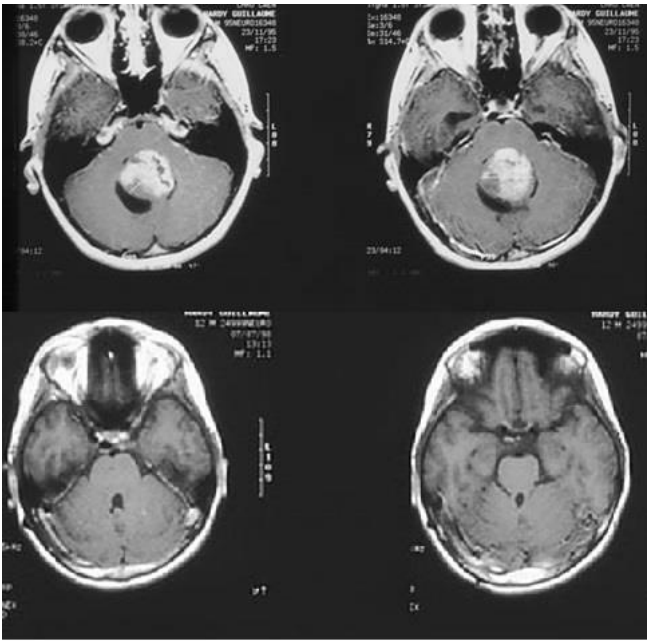

Figure 7. Cystic astrocytoma of the right cerebellar hemisphere, total ablation pre- and postoperative
(Personal collection of Prof. Dr. A. V. Ciurea)

Often the surgical treatment consists only of palliative procedures that address only the increased ICP phenomena (exp.: CSF diversion procedure – external ventricular drainage), with radiotherapy as the next step to stop the tumor progression (exp.: basal ganglia tumor). The surgical treatment must be associated with corticotherapy such as dexamethazone and cerebral depletion drugs, especially in high grade gliomas, for their anti-edema effect.

Cerebral biopsy

Cerebral biopsy is a surgical procedure that is part of the surgical treatment of the primary tumor, or it can be a separate diagnostic tool. As a diagnostic tool is it indicated for cerebral areas considered inoperable and is performed with a cerebral biopsy needle through a burr hole. Two different procedures for performing a cerebral biopsy are available today:

- Stereotaxic biopsy – bases on information following CT and MRI images corroborated, precise guidance of biopsy of the cerebral tumor is acquired, the head is pinned into a compass-like device and coordinates are used to guide the trajectory of the biopsy needle
- Biopsy guided by the neuronavigation system, with the advantage that is does not need the head to be pinned in a compass-like device.

9. Radiotherapy

Radiotherapy has major impact in radio-sensitive malignant cerebral tumors such as medulloblastomas, ependymomas, metastasis, but it is also done in other intracranial tumors: pituitary tumor, acoustic neuromas, meningiomas. The combining of surgical treatment, radiotherapy and chemotherapy designate the multimodal treatment with increased efficiency in aggressive cerebral tumors.

The use of hyper voltage radiotherapy with fascicles focused strictly on the tumoral lesion constitutes the stereotactic radiotherapy, which includes „gamma knife" (GKS) and LINAC and which is done as single therapy, postoperative or as part of multimodal schemes and in recurrence cases. Radiotherapy acts in M, G2 phase of cell mitosis.

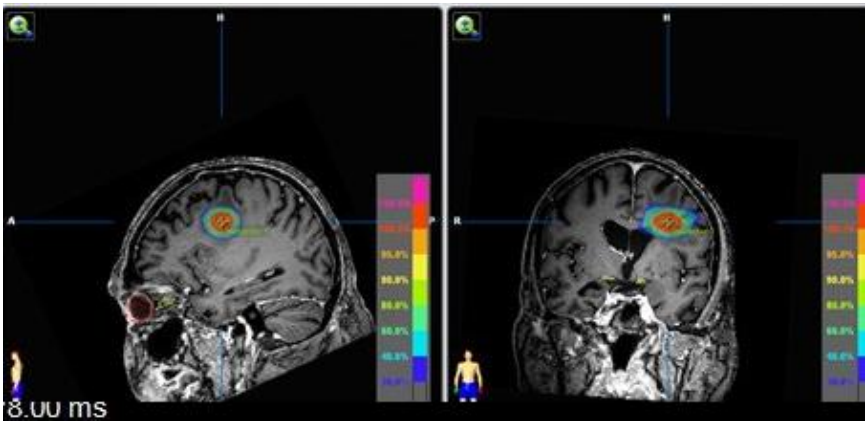

Figure 8. Radiotherapy in brain tumors
(Personal collection of dr. Vicențiu Săceleanu)

Radiotherapy in not indicated under the age of 3 is to be done under great attention in toddler patients due to global brain irradiation and possible local radionecrosis.

The younger the cells within the tumor, the more efficient the radiotherapy is, so that considering this classification medulloblastomas are the most sensitive to radiotherapy.

10. Chemotherapy

Chemotherapy based on cytostatics is indicated in high grade tumors after surgical treatment and simultaneously of after radiotherapy to prevent recurrence and dissemination through CSF. Multimodal treatment schemes that include a surgical resection as wide as possible, radiotherapy and chemotherapy have an increased efficiency in malignant cerebral tumors.

Liposoluble and low molecular weight chemotherapy drugs can penetrate the blood-brain barrier, but they cannot penetrate the central and necrotic area of the tumor. Various chemotherapy agents are in use: nitrosourea derivates – liposoluble and that penetrate the blood-brain barrier, procarbazine, vincristine, cyclophosphamide, in monotherapy or complex schemes.

11. Immunotherapy

Immunotherapy, monoclonal antibodies can be used as carriers of toxic agents, the cellular immune system being manipulated by the use of exogenous biological response modifiers, or by transferring the activated lymphocytes.

12.Photodynamic therapy

Photodynamic therapy uses the photosensitive substances, which once introduced in organism are fixed on the tumour cells, then through laser excitation of a particular wavelength, the substance is activated, resulting in the death on the cells which the substance has been fixed on. The substances used must not be toxic to the human body, be absorbed selectively detected by fluorescence type techniques, and be effective in destroying the tumour cells.

13. Hyperthermia

Hyperthermia may be:

- Intratumoral local;
- Regional;
- Thermal gradient;
- Total hyperthermia.

14. Prognosis

The prognosis is influenced by the histopathology of the tumor and because most of them are of neuroectodermal origin (over 60%) and some present with high malignancy or are of an extremely infiltrative nature (brainstem glioma or hypothalamic glioma) the prognosis is severe in a large percentage of cases. Difficult surgical approach of median tumors further adds to a severe prognosis.

A better prognosis is estimated for cerebral of cerebellar hemispheric tumors, because of their benign or low malignancy histopathology (pilocytic astrocytoma, benign oligodendroglioma) and because of their less difficult surgical approach. Meningiomas are mainly benign tumors, and their prognosis is very good especially if a complete resection is performed, without affecting the brain parenchyma.

A considerable group of tumors are of benign histopathology, but also of deep, median or skull base anatomical, which makes the neurosurgical procedure a high-risk surgery (exp: craniopharyngiomas, chordomas or clival meningiomas). Multiple neurological impairment and psychiatric impairment is to be considered in children that have had cerebral tumors surgically removed.

Prognosis appreciation when it comes to the post-surgical evolution of intracranial tumors is acquired objectively using various scales. The most often used is the GOS (Glasgow Outcome Scale). (Table 1) (18)

Table 1. Glasgow Outcome Scale (GOS)

Score	Description
1	Death
2	Persistent vegetative status – no obvious cortical function
3	Severe disability – conscious, but with major deficit, dependent and in need of permanent support
4	Moderate disability – disability is present, but the patient is independent in regard to daily activities (exp: aphasia, hemiparesis, ataxia, memory, personality or intellectual deficit)
5	Good recovery – patient resumes daily activities with minor or no neurological or psychic deficits

15. Conclusions

Intracranial tumors are an extremely difficult problem therapeutically speaking. The microsurgical treatment is mainly the elective treatment, a complete resection being the main goal (17). This can be achieved under very good conditions, almost perfect conditions when it comes to benign tumors (exp: posterior fossa pilocytic astrocytoma, craniopharyngioma, acoustic neuroma, meningiomas etc. (Figures 9 and 10)

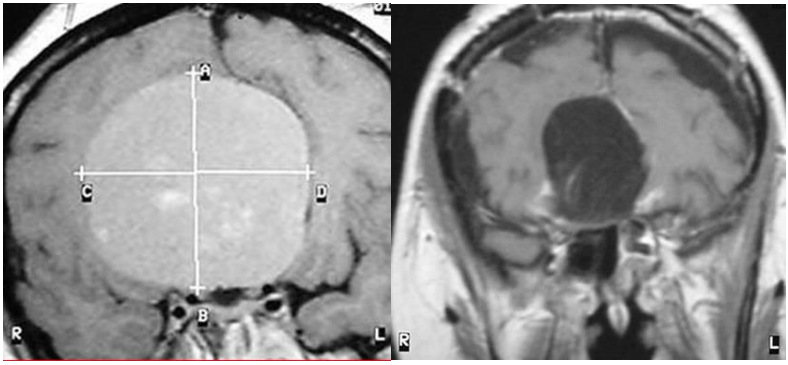

Figure 9. MRI: gigantic olfactory groove meningioma, pre- and post-operative
(Personal collection of Prof. Dr. A. V. Ciurea)

In the case of benign intracranial pathology such as meningiomas, acoustic neuromas, hemangioma, low-grade astrocytoma, oligodendrogliomas, all efforts to achieve complete resections must be done but definitely with perfect preservation of quality of life (Figure 22 a and b). The main principal in neurosurgery today is "maximum safe resection"; never should we insist on excisions that can affect eloquent or vital areas (brainstem). (19)

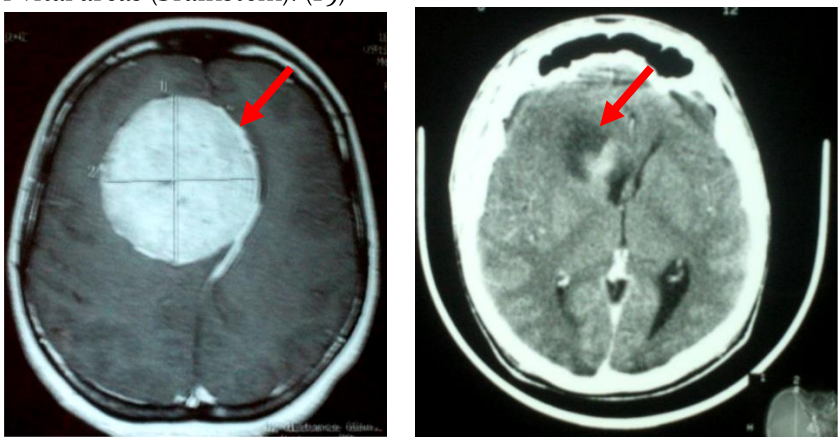

Figure 10. MRI: gigantic right frontal meningioma, pre- and post-operatory
(Personal collection of Prof. Dr. A. V. Ciurea)

When it comes to infiltrative tumors such as high-grade astrocytoma, microsurgical resection cannot always insure complete ablation. Therefore, adjuvant treatment such as radio- and chemotherapy is required. This type of patient needs to be monitored with follow-up plain and contrast enhanced MRI and if local tumor regrowth occurs a new surgical resection is to be considered, as extended as possible and without damaging eloquent areas (speech area, motor area, etc.).

Abbreviations: **CT** – computerized tomography*;* **CSF** – cerebrospinal fluid; **GKS**- gamma knife surgery*;* **ICP** – increased intracranial pressure*;* **ICT** – intracranial tumors*;* **MRI** – magnetic

resonance imaging; **NPH** – normal pressure hydrocephalus; **SAH** – subarachnoid hemorrhage

Disclaimer: The authors have no conflicts of interest to declare.

References:

1. Arseni C., Carp N., Anatomia patologică a tumorilor sistemului nervos, Editura Didactică și Pedagogică, București, 1978.
2. Arseni C., Horvath L, Ciurea A.V., Patologie neurochirurgicală infantilă, Ed. Acad. RSR,1980.
3. Bailey P., Cushing H., A classification of the tumors of the glioma group on a histogenic basis with a correlated study of prognosis, Lippincott, Philadelphia, 1926.
4. Ciurea A.V., Tratat de Neurochirurgie Vol. 1, Editura Medicală, București, 2010.
5. Ciurea A.V., Tratat de Neurochirurgie Vol. 2, Editura Medicală, București, 2011.
6. Ciurea A.V., Iencean S., Tumorile intracraniene în Irinel Popescu Tratat de Chirurgie, Vol II - Neurochirurgie, Ed. Academiei Române, București, 2007.
7. Ciurea A.V., Voinescu D., Nuteanu L., Zamfir C., Craniopharyngiomas - a study of 58 cases, Romanian Neurosurg, 2:173-81, 1992.
8. Ciurea A.V, Iencean S., Mohan D., Simptomatologia tumorilor intracraniene, în Actualități în tumorile intracraniene, Editura Universitară, București, 2011.
9. Constantinovici A., Ciurea A.V., Ghid practic de neurochirurgie, Ed. Medicală, Bucureşti, 1998.
10. Haddad G.F., Al-Mefty O., Meningiomas: an overview. In: Wilkins R.H., Rengachary S.S., Eds., Neurosurgery, 2nd ed. Vol 1., New York, NY, McGraw-Hill, 833-42, 1996.
11. Iencean S., Ciurea A.V., Tumori intracraniene în Tratat de Neurochirurgie, Vol. I, Ed. Medicală, București, pg. 388-433, 2010.
12. Kleihues P., Cavanee W., WHO classification of tumours, In Pathology and Genetics: Tumours of the Nervous System, Lyon, France, IARC, 2000.
13. Kaye A.H., Walker D.G., Low-grade glial neoplasms în Neurological surgery, principles and practice, Hunt Batjer H., Loftus C.M., Lippincott Williams & Wilkins, 2003.

14. Laws E.R., Thapar K., Craniopharyngiomas in children and adults în Neurological surgery, principles and practice, Hunt Batjer H., Loftus C.M. Eds., Lippincott Williams & Wilkins, 2003.
15. Samii M., Matthies C., Management of 1000 vestibular schwannomas (acoustic neuromas): surgical management and results with emphasis on complications and how to avoid them, Neurosurgery, 40:11-21, discussion 21-13, 1997.
16. Schmidek H.H., Roberts D.W., Operative Neurosurgical Techniques, 5th Edition - Indications, Methods and Results, Saunders, 2006.
17. Yasargil M.G., Curcic M., Kis M., Total removal of craniopharyngiomas. Approaches and long-term results in 144 patients, J Neurosurg, 73(1): 3-11, 1990.
18. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. Mar 1 1975;1(7905):480-4
19. Ciurea A.V., Iencean MS, Mohan A, Moisa A, Our policy in Olfactory Groove Meningiomas. New standards of care, Quality of Life and Global Outcome, 15th Interim Meeting of the World Federation of Neurosurgical Societies, 8-12 Septembrie 2015.

INTRACRANIAL MENINGIOMAS

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I never teach my pupils; I only attempt to provide the conditions in which they can learn
Albert Einstein (1879-1955)

Contents

1. Introduction. Epidemiology

Meningiomas are benign tumor of the meninges. It constitutes approximately 15% of all intracranial tumours and presents the most increased incidence in the seventh decade; it is rare in children but more common in women. Although histopathologically benign, some

meningiomas often behave as malignant tumors, tending to recur, even after complete removal. A meningioma compresses and does not invade the surrounding nervous tissue (1).

Most meningiomas are supratentorial. Their topographic site corresponds to the distribution of Pacchioni's granulations, in the proximity of the venous sinuses and of the bony insertions of the dura mater. By site, there are parasagittal meningiomas, brainstem, cerebral hemisphere convexities, lateral ventricular meningiomas, and meningiomas at the base of the skull, such as those of the olfactory groove (Figure 1) and of the sellar tubercle.

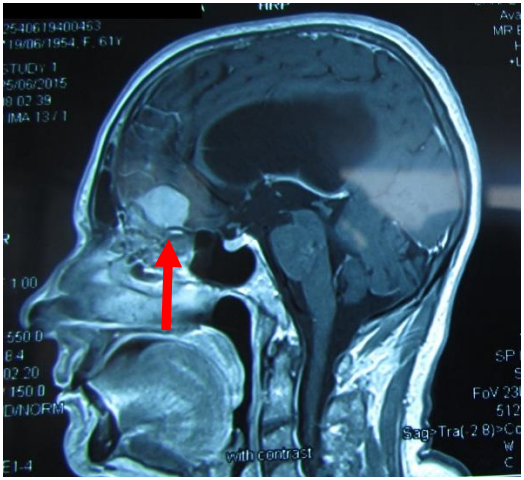

Figure 1. MRI: olfactory groove meningioma (Personal collection of Prof. Dr. A. V. Ciurea)

A special form of meningiomas is intraventricular meningiomas, common in children.

Ectopic meningiomas have been cited in the literature - inside the skull bones (primary intraosseous meningioma), while others are found in the subcutaneous tissue without being attached to the skull (2,3).

Sometimes forms of meningiomas with multiple lesions can be found - meningiomatosis. (Figures 2, 3) - neurofibromatosis type II.

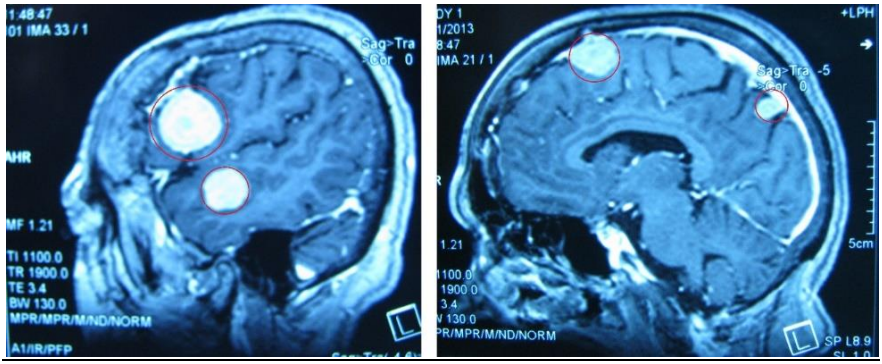

Figure 2. MRI aspect of multiple meningiomas (meningiomatosis)
(Personal collection of Prof. Dr. A.V. Ciurea)

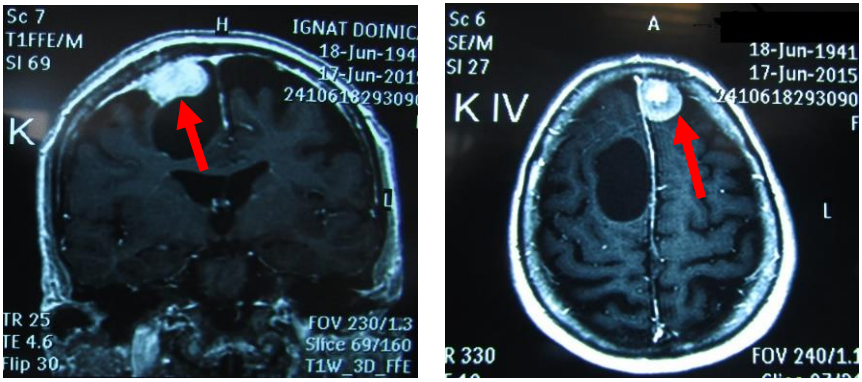

Figure 3. MRI: multiple convexity meningiomas
(Personal collection of Prof. Dr. A. V. Ciurea)

2. Morphopathology

Meningiomas can develop on both sides of the dura mater, but especially on its inner face. (Figure 4)

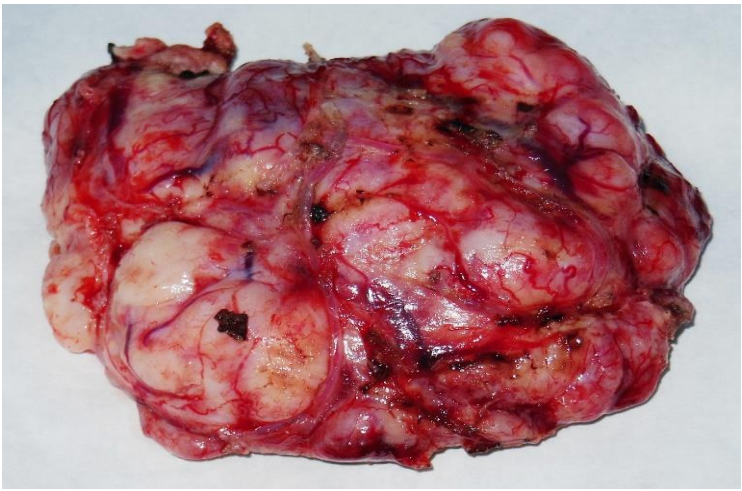

Figure 4 Morphopatological appearance of the convexity meningioma (Personal collection of dr. Vicențiu Săceleanu)

Meningiomas come in two forms: round and flat ("en plaque"). Round meningioma is found mainly on the convexity of the brain or intraventricular, where growth in all directions is free. The flat meningioma is flattened and stretched and adheres to the dura mater over a large area, and its thickness is small compared to its insertion base. It develops mainly at the base of the skull, being accompanied in this case by a marked hyperostosis. This type of meningioma is exceptional in children. Meningiomas are benign tumors (meningothelial, fibroblastic, transitional, psammomatous, angiomatous, microcystic, secretory, clear cell, chordoid), semi-malignant (atypical, papillary meningioma), and malignant (anaplastic). Meningiomas frequently include intratumoral calcifications, being described from a histopathological point of view of psammomatous bodies.

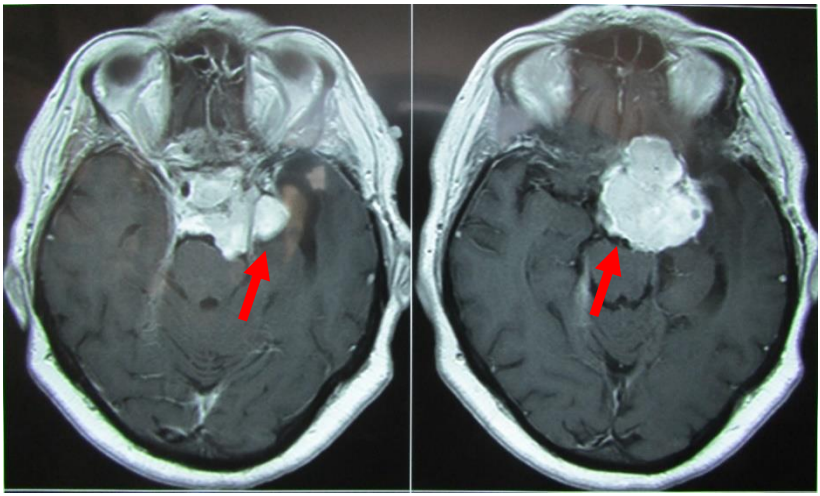

Figure 5. MRI: giant meningioma of the sphenoid, smaller wing with fronto-temporal expansion
(Personal collection of Prof. Dr. A. V. Ciurea)

3. Classification

By size, meningiomas are classified into:

- small (up to 2 cm in diameter, often multiple)
- medium (between 2-4 cm diameter)
- large (4-6cm diameter)
- giant (over 6 cm in diameter).

Meningiomas are benign tumors developed from the meningothelial cells of the arachnoid.

In frequency, it represents 20% of primitive intracranial tumors, being on the second place after gliomas. It is a middle-aged tumor and predominantly affects women.

Usually, a meningioma is a solitary tumor, but sometimes multiple meningiomas are discovered, and can form a true meningiomatosis with many tumors of varying size.

There are particular clinical cases in which meningioma has multiple locations in the same patient. Multiple meningiomas within type II neurofibromatosis is the most common such situation. About half of patients with type II neurofibromatosis develop at least one

meningioma in their lifetime, which is why an individual who presents as suspect or is found to have more than one meningioma should be investigated for this condition, including an extended family history (4,5).

Classifications based on the topography of the lesion and the histopathological grade will be noted according to the 2016 WHO Brain Tumor Classification (8).

The topography of the intracranial disposition of the meningioma conditions the neurological semiology and is at the origin of various anatomo-clinical classifications. (9) According to these criteria, meningiomas are divided into:

1. Convexity meningiomas
2. Skull base meningiomas
3. Parasagittal meningiomas (the base of implantation is in relation to the superior sagittal sinus). The term parasagittal meningioma can be used when no intact brain tissue is interposed between the superior sagittal sinus and the tumor.
4. Falx cerebri meningiomas, with unilateral or bilateral development

Most brain scarring meningiomas originate in the proximity of the paracentral lobe. Tumors with this localization are neurologically associated with unilateral or bilateral crural monoparesis in case of increased volume.

5. Tentorial meningioma
6. Posterior cerebral fossa meningiomas.

The classification of meningiomas is done according to their anatomical situation: supratentorial and infratentorial. Each of them is delimited by the area of dural insertion of the meningioma: brainstem, olfactory grooves, small wing of the sphenoid, infratemporal, basal dura mater, tentorium, petro-clival, pontocerebellar angle, etc.

From the anatomopathological point of view, the classification of meningiomas according to the Classification of the World Health Organization adopted in 2016 is currently used.

Cranial classification of meningioamas according to WHO classification of 2016

Table 1. Histopathological classification of meningiomas

Grade 0 – benign	**Grade 1 – borderline or cannot be appreciated**	**Grade 2 – carcinoma in situ or epithelial neoplasms**	**Grade 3 – malignant**
Meningothelial fibrous transitional psammomatos microcystic angiomatos secretory lymphoplasmocytes-rich metaplastic	Choroid with clare cells atipycal	-	Papillary rabdoid anaplastic

Sindou classification of parasagittal meningiomas (15)

Table 2. Sindou classification of parasagittal meningiomas

Sindou grade	**Description**
I	Attached to the lateral wall of the superior sagittal sinus
II	Invasion of lateral recces
III	Invasion of lateral wall
IV	Invasion of lateral wall and superior wall
V	Complete sinus occlusion with contralateral wall uninvolved
VI	Complete sinus occlusion, invasion of all its walls

4. Clinical data

The entire neurological semiology depends on the size of the meningioma and the location relative to the tumor implantation base. Meningiomas may precede the neurological signs by to 10-15 years of evolution, which shows their slow growth rate.

The onset is often monosymptomatic with headache, motor or sensory jacksonian epileptic seizures, or facial neuralgia.

Signs and symptoms of intracranial hypertension are rare in the classic version of the triad, appearing only in the case of intraventricular meningiomas with secondary hydrocephalus (6,7).

Depending on the topography of the tumor, a focal neurological syndrome is outlined. The following aspects are described for it:

- progressive extension and slow evolution
- consisting of several clinical disorders:
- or contralateral motor deficit (with upper motor neuron syndrome)
    - *Gerstmann syndrome* (parietal lesion of the dominant hemisphere – commonly the left one)

      Gerstmann syndrome consists of 4 components: agraphia, acalculia, digital agnosia and left-tight disorientation. It is due to lesions in the lower parietal lobule of the dominant hemisphere, supramarginal and angular gyrus, corresponding to Broadmann areas 39 and 40, respectively.
    - an Anton-Babinski syndrome (right parietal lesion)

It consists in the sensitive neglect of the contralateral hemibody, anosognosia, with indifference without the existing deficit, constructive apraxia or dressing.

- aphasic disorders
- homonymous lateral hemianopsia
- psychiatric disorders
- late and focused epilepsy
- cerebellar syndromes.

Skull base meningiomas affect the cranial nerves through and in the vicinity of the implantation area. Based on these considerations, the following neurological syndromes are described.

- *olfactory groove meningioma:* anosmia (C.N. I).
- *anterior clinoid process meningioma, lower wing of sphenoid in its internal third or the optic canal*

Foster-Kennedy syndrome – unilateral blindness with papillary atrophy and contralateral papillary hypertrophy.

- *meningioma of the sphenoid, internal third of the lower wing*

Cavernous sinus syndrome – unilateral ophthalmoplegia (paresis of ipsilateral C.N. III, IV, VI), Horner syndrome (miosis, superior eye lid ptosis, anophthalmia, anhidrosis of the ipsilateral half face) and sensory deficit within ophthalmic and maxillary nerves territory

- *temporal apex meningioma* - trigeminal neuralgia and paresis pf masticatory muscles (C.N. V) – secondary to compression of trigeminal ganglion of Gasser into the Meckel fossa
- *cerebello-pontine angle meningioma:* unilateral perception hearing loss which is progressive (C.N. VIII) or involvement of cranial nerves that cross through the jugular foramen in lower development into the cerebello-pontine angle

Vernet syndrome*– paresis of ipsilateral cranial nerves IX, X,XIl.*

- *clival or posterior cerebral fossa meningioma:* simulates a brainstem tumor that progressively affects much or less all the cranial nerves.

Collet-Sicard syndrome *– paresis of ipsilateral cranial nerves IX, X, XI, XII.*

Gracin syndrome*– paresis of ipsilateral cranial nerves III-XII.*

These last two syndromes are very little particular or revealing for a meningioma in the posterior cerebral fossa, but they are to be noted for their extremely important neurological value.

Meningiomas can also cause clinical signs that are tributary to neighboring bone reactions. They may be the first signs of the tumor and materialize in a generally painless bony swelling of the cap or unilateral exophthalmos in meningiomas "en plaque".

5. Paraclinical diagnosis in meningiomas

Brain CT examination is the essential examination sufficient, most of the time, for diagnosis. Native examination shows an isodense or

discrete hyperdense lesion. After injection contrast agent, the tumor appears intensely hyperdense. They have a direct connection with the brain layers or cranial vessels, strongly and uniformly capturing the contrast substance highlighting the so-called ***dural tail,*** which is characteristic of these tumours. They may be surrounded by a focal peritumoral edema but a minimal mass effect. A very important sign is thickening and hyperostosis of the bone cap portions in contact with the tumour.

Brain CT examination specifies the size of the tumor, the basis of implantation, topography, peritumoral edema and the mass effect produced by the tumor.(Figure 6)

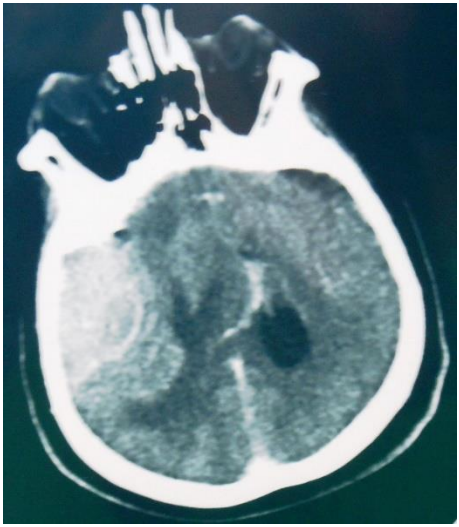

Figure 6. C.T. scan appearance, sphenoid wing meningioma (Personal collection of dr. Vicențiu Săceleanu)

MRI examination is very useful, especially in basic cranial meningiomas, to determine relationships with cranial vessels and nerves. (Figure 7,8)

Digital subtraction angiography is required for preoperative study and evaluation of tumor vascularization. Regarding meningiomas developed in the intimate proximity of the cerebral venous sinuses,

angiography provides valuable information about their degree of invasion and their patent.

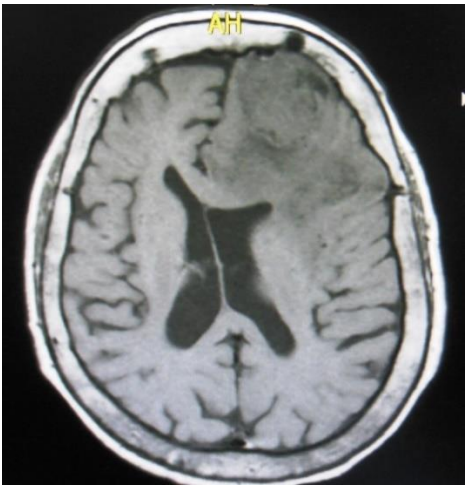

Figure 7. Left frontal meningioma, MRI examination without contrast agent
(Personal collection of dr. Vicențiu Săceleanu)

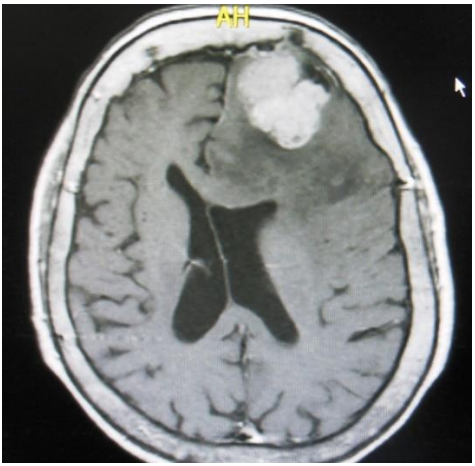

Figure 8. MRI appearance with contrast agent, left frontal meningioma
(Personal collection of dr. Vicențiu Săceleanu)

Cranial radiography frequently reveals meningioma calcifications, hyperostosis, or destruction of the internal plaque.

Other complementary examinations may be required depending on the clinical picture:

- the ENT exam
- ophthalmological examination
- auditory evoked potentials (in meningiomas of the pontocerebellar angle).

6. Treatment of meningiomas

In most cases, neurosurgical treatment of these tumors can be extremely difficult, due to the multiple implications of nerve and vascular formations.

Being a generally benign tumor, surgical excision is the only curative treatment.

Small meningiomas, with modest symptoms, in an elderly or crippled patient, may benefit from simple clinical surveillance and serial imaging examinations (brain MRI) to monitor the dimensional evolution. (10)

Surgical treatment addresses symptomatic small meningiomas with unsatisfactory drug control of symptoms and large meningiomas due to the potential for lesional evolution.

Because meningiomas usually have vascularization from branches of the external carotid artery, angiography can be used as a first therapeutic time, allowing the embolization of arterial pedicles by supraselective catheterization. Meningioma embolization facilitates surgical ablation and its duration by varying the reduction of bleeding. (10,11,12)

Simpson resection score

An important element is the assessment of the ***Simpson score of postoperative resections.*** It correlates with the risk of symptomatic recurrence of meningioma calculated at 10 years (16).

Table 3. Simpson resection score

Simpson resection score	**Descriptions**	**Risk of symptomatic recurrence after 10 years**
0	I + excision of dural insertions with unaffected margins and 2 cm around it	**<1%**
I	Total macroscopic ablation, excision of dural insertion and of abnormal bone, including venous sinus resection if involved	**9%**
II	Total macroscopic ablation, dural insertion coagulation	**19%**
III	Total macroscopic ablation of intradural tumor, without resection or coagulation of dural insertion or extradural extension	**29%**
IV	Partial ablation, with intradural in-situ rest of tumor	**44%**
V	Tumor reduction, with or without biopsy	**100%**

In ablation surgery of cerebral meningiomas there are four principles: early suppression of tumor vascularization, internal tumor decompression / reduction, dissection of the tumor capsule from the brain tissue, resection / coagulation of the dura and removal of the modified neighboring bone when possible.

The therapeutic approach consists of microscopic total resection (Kobayashi) to prevent recurrences. The dura mater is also resected, which is adjacent and infiltrated, removing the infiltrated bone portions followed by bone and dural plasty. (figure 9)

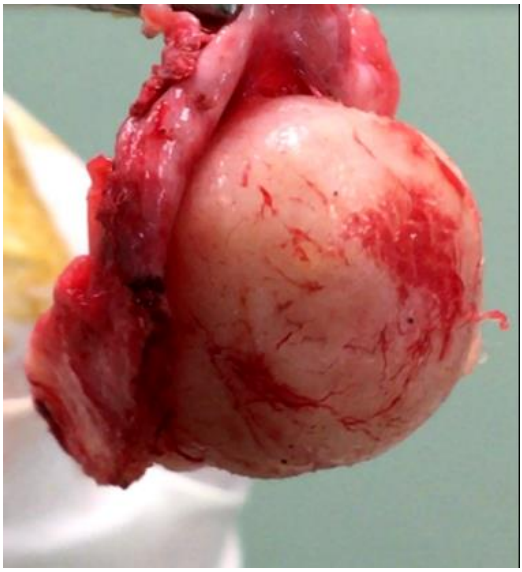

Figure 9. Complete resection
(Personal collection of dr. Vicențiu Săceleanu)

Conventional radiotherapy is recommended is cases of tumor regrowth, anaplastic meningiomas and when only a biopsy was performed.

Multifascicular radiotherapy „gamma knife" is to be performed in cases of small meningiomas of less than 3 cm in diameter, with sites that makes any surgical approach to be a high risk one. Hormonal therapy is considered a supportive treatment after an incomplete resection or in cases of tumor recurrence.

7. Conclusion

Although they are mainly benign tumors and do not invade brain tissue, due to their site meningiomas can pose serious problems related to the surgical approach, invasion of structures with high or recurrent functional importance.

Unlike gliomas, where improvements in surgical treatment have been made to a lesser extent in the latest decades, remarkable progress has been made in the surgical treatment of meningiomas, allowing a

complete surgical resection with almost perfect preservation of neighboring tissue, while respecting venous distribution. and CSF circulation routes.

Abbreviations: **CT** – computerized tomography**;** **MRI** – magnetic resonance imaging**;** **WHO** – World Health Organization

Disclaimer: *The authors have no conflicts of interest to declare.*

References:

1. Arseni C., Carp N., Anatomia patologică a tumorilor sistemului nervos, Editura Didactică și Pedagogică, București, 1978.
2. Arseni C., Horvath L, Ciurea A.V., Patologie neurochirurgicală infantilă, Ed. Acad. RSR,1980.
3. Ciurea A.V., Tratat de Neurochirurgie Vol. 1, Editura Medicală, București, 2010.
4. Ciurea A.V., Tratat de Neurochirurgie Vol. 2, Editura Medicală, București, 2011.
5. Ciurea A.V., Iencean S., Tumorile intracraniene în Irinel Popescu Tratat de Chirurgie, Vol II - Neurochirurgie, Ed. Academiei Române, București, 2007.
6. Ciurea A.V, Iencean S., Mohan D., Simptomatologia tumorilor intracraniene, în Actualități în tumorile intracraniene, Editura Universitară, București, 2011.
7. Constantinovici A., Ciurea A.V., Ghid practic de neurochirurgie, Ed. Medicală, Bucureşti, 1998.
8. Haddad G.F., Al-Mefty O., Meningiomas: an overview. In: Wilkins R.H., Rengachary S.S., Eds., Neurosurgery, 2nd ed. Vol 1., New York, NY, McGraw-Hill, 833-42, 1996.
9. Iencean S., Ciurea A.V., Tumori intracraniene în Tratat de Neurochirurgie, Vol. I, Ed. Medicală, București, pg. 388-433, 2010.
10. Kleihues P., Cavanee W., WHO classification of tumours, In Pathology and Genetics: Tumours of the Nervous System, Lyon, France, IARC, 2000.
11. Schmidek H.H., Roberts D.W., Operative Neurosurgical Techniques, 5th Edition - Indications, Methods and Results, Saunders, 2006.
12. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. Mar 1 1975;1(7905):480-4

13. Ciurea A.V., Iencean MS, Mohan A, Moisa A, Our policy in Olfactory Groove Meningiomas. New standards of care, Quality of Life and Global Outcome, 15th Interim Meeting of the World Federation of Neurosurgical Societies, 8-12 Septembrie 2015.
14. Goutagny S, Kalamarides M. Meningiomas and neurofibromatosis. J Neurooncol. 2010 Sep;99(3):341-7, Epub 2010 Aug 17
15. Ricci, Alessandro et al. "Parasagittal meningiomas: Our surgical experience and the reconstruction technique of the superior sagittal sinus." *Surgical neurology international* vol. 8 1. 19 Jan. 2017
16. Kinjo T, al-Mefty O, Kanaan I. Grade zero removal of supratentorial convexity meningiomas. Neurosurgery. 1993 Sep;33(3):394-9.

CEREBRAL GLIOMAS

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Nunc Minerva, postea Palas Atenea
(First wisdom, after the war) – Unknown military engineer

Contents

1. Definition

Gliomas arise from the glial component of the nervous system and represent the most common brain tumors, being responsible for about 40% of all brain neoplasms. In general, glial tumors are named after the cells from which they originate (astrocytomas, oligodendrogliomas, ependymomas), there is a great diversity in terms of clinical, histological data and therapeutic response, thus emphasizing the variety of genes involved in genesis. (1)

2. Classification

Astrocytes can be classified according to the degree of abnormalities. The best-known grading system uses a scale from I to IV. Tumors can also be grouped by growth rate: low-grade (slow growth), mid-grade (moderate) and high-grade (fast).

The WHO classification of brain tumors is based on the degree of malignancy and the invasiveness of these tumors. Tumors with a high degree of invasiveness, which often undergo genetic mutations, are graded with a higher number. According to the WHO, grade I applies to lesions with low proliferative potential and the possibility of complete healing after surgical resection. Grade II brain neoplasms are generally infiltrative in nature and, despite the rather low degree of proliferation, give relapses. Certain grade II tumors tend to progress to higher degrees of malignancy, for example, low-grade diffuse astrocytomas that can evolve into anaplastic astrocytomas and glioblastomas. Grade III is generally reserved for lesions with clear histological evidence of malignancy, including nuclear atypia and increased mitotic activity. In most cases, patients with grade III brain tumors after surgery receive adjuvant radiotherapy and / or chemotherapy. Grade IV is attributed to cytologically malignant brain tumors, with increased mitotic activity, tendency to tissue necrosis, with inflammatory tissue infiltrate, associated with an unfavorable evolution towards exitus, evolution slowed by applied multimodal treatment. Grade IV brain tumors include glioblastomas and many sarcomas.

In this classification based on the histopathological examination we find:

- **Benign gliomas:**

Grade I glioma - considered benign, having as curative treatment surgical excision. They generally appear in childhood.

Grade II gliomas are usually considered "low-grade" and classified as benign, but often this type of glioma tends to be recurrent.

- **Malignant gliomas:**

Grade III glioma: also called anaplastic astrocytoma (anaplastic means malignant) is a mid-grade, diffuse and infiltrative tumor with a higher tumor growth rate than grade I and II gliomas. The histopathological diagnosis is based on the appearance of nuclear atypia and mitotic activity.

Grade IV glioma: also abbreviated GBM or glioblastoma multiforme is the most malignant form of astrocytoma. The factor that differentiates glioblastoma from anaplastic astrocytoma is the presence of necrosis (dead cells) and increase of abnormal growth of blood vessels around the tumor (angiogenesis). The name "glioblastoma multiforme" is related to the polymorphism of macroscopic, microscopic and genetic aspects, extremely aggressive and resistant to current therapies.

The latest classification of brain tumors given by the World Health Organization in 2016 divides gliomas both in terms of histopathological diagnosis (the IV degrees presented above) and in terms of genetic profile. This leads to an accurate diagnosis and the beginning of a treatment and personalized management for each type of pathology.

For example, tumors with methylated MGMT (inactive gene) have been found to predict a longer length of survival and responds better to chemotherapeutic agents in the treatment of glioblastoma.

From a genetic point of view:

WHO grade III anaplastic astrocytomas are divided into IDH-mutant, IDH-wildtype.

Grade III gliomas without IDH- mutant could be considered “pre-glioblastomas”, having a poorer prognosis than IDH mutant tumors. IDH mutations tend to occur in younger brain tumor cases, most commonly between the ages of 20 and 40, with a median age at diagnosis in the 30s.

There are two subtypes of glioblastoma:

1) glioblastoma, **IDH-wild type (90%)**, frequently defined as primary or de novo predominated in patients over 55 years of age.

2) glioblastoma, **IDH- mutant (10%)** which called secondary with malignant transformation from low grade glioma, common in younger patients under 45 years old.

IDH wild type glioblastomas exist in 3 forms:

1. Giant cell glioblastomas
2. Gliosarcomas
3. Epithelioid glioblastomas; (newly introduced in WHO 2016)

There are forms that are difficult to diagnose in terms of molecular information and they fall into the category of **NOS glioblastomas (not otherwise specified) - nonspecific.**

WHO classification 2016
Layer 1:
Integrated diagnosis

Layer 2:
Histological diagnosis

Layer 3:
WHO degree

Layer 4:
Molecular information

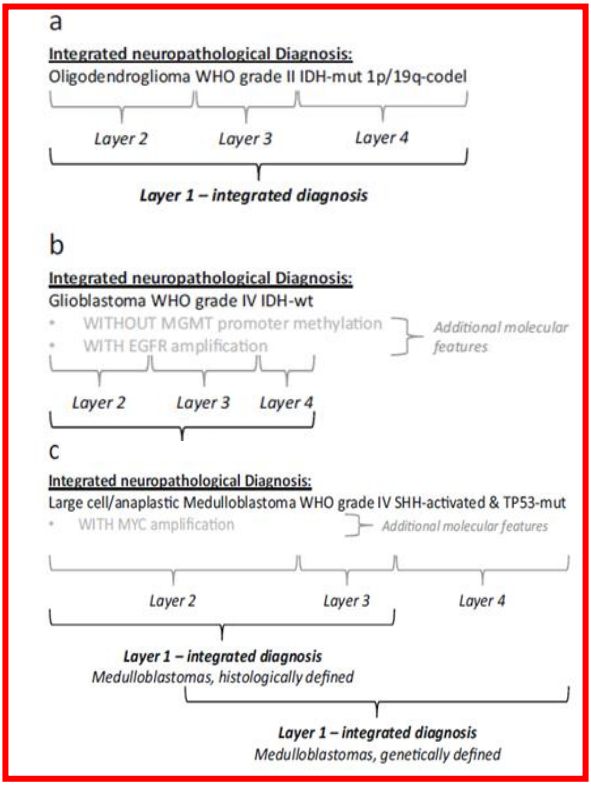
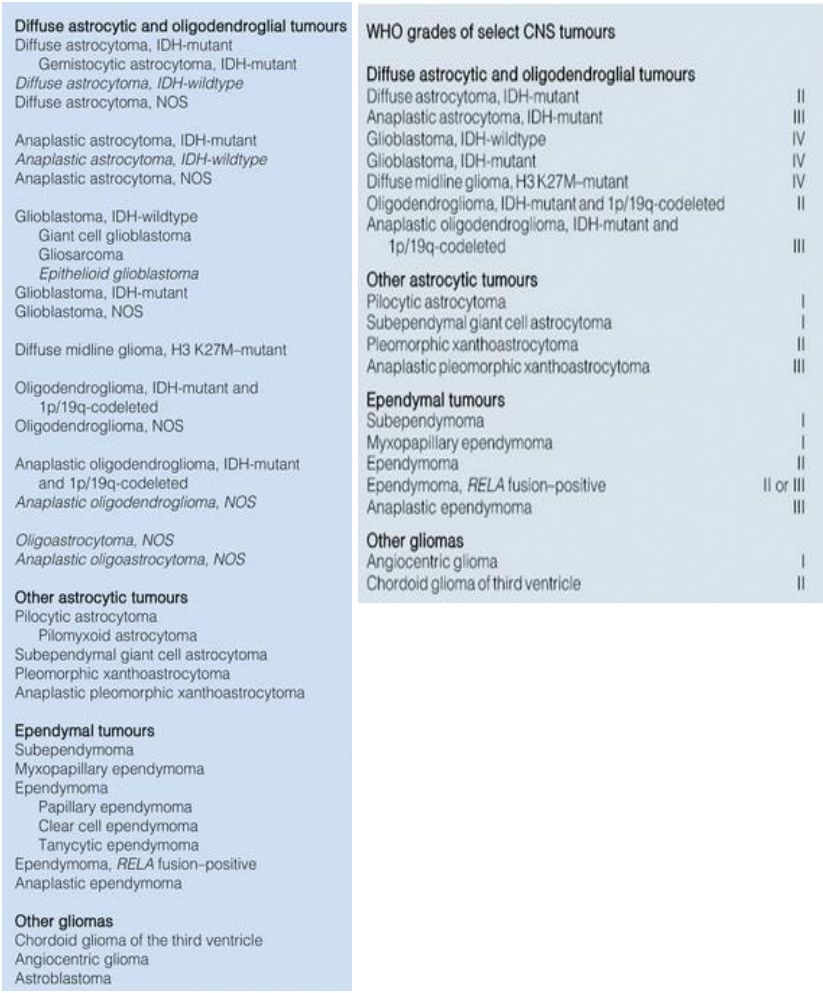


Figure 1. Diagnostic examples according to WHO 2016 (Image source: Modified from (1))



Diffuse astrocytic and oligodendroglial tumours
Diffuse astrocytoma, IDH-mutant
Gemistocytic astrocytoma, IDH-mutant
Diffuse astrocytoma, IDH-wildtype
Diffuse astrocytoma, NOS

Anaplastic astrocytoma, IDH-mutant
Anaplastic astrocytoma, IDH-wildtype
Anaplastic astrocytoma, NOS

Glioblastoma, IDH-wildtype
Giant cell glioblastoma
Gliosarcoma
Epithelioid glioblastoma
Glioblastoma, IDH-mutant
Glioblastoma, NOS

Diffuse midline glioma, H3 K27M–mutant

Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
Oligodendroglioma, NOS

Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted
Anaplastic oligodendroglioma, NOS

Oligoastrocytoma, NOS
Anaplastic oligoastrocytoma, NOS

Other astrocytic tumours
Pilocytic astrocytoma
Pilomyxoid astrocytoma
Subependymal giant cell astrocytoma
Pleomorphic xanthoastrocytoma
Anaplastic pleomorphic xanthoastrocytoma

Ependymal tumours
Subependymoma
Myxopapillary ependymoma
Ependymoma
Papillary ependymoma
Clear cell ependymoma
Tanycytic ependymoma
Ependymoma, *RELA* fusion–positive
Anaplastic ependymoma

Other gliomas
Chordoid glioma of the third ventricle
Angiocentric glioma
Astroblastoma

WHO grades of select CNS tumours

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M–mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion–positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II

Figure 2 and 3. WHO 2016 glioma classificatio n
(Image source: modified from (1))

3. Incidence

About 50% of gliomas are glioblastomas. They are most common in adults ages 45–65, and affect more men than women. Glioblastomas arise from normal brain tissue. They may invade and migrate away from

the main tumor within the brain; however, glioblastoma will rarely spread elsewhere in the body.

In most states in Europe and North America, the annual incidence reaches 2-4 new cases per 100,000 inhabitants per year. (2)

4. Etiological factors

The etiology of gliomas is largely unknown, but there are several theories about the appearance of gliomatous cells:

- perinatal viral origin
- various mutations of protooncogenes
- mutations in tumor suppressor genes
- mutations of chromosomes 10 and 17

The only factor whose influence could be demonstrated by extensive epidemiological studies is radiotherapy. In this case the risk of producing an infiltrative glioma is 16-20 times higher.

Risk factors associated with the appearance of gliomas:

- sex: men are slightly more frequently affected by this pathology than women
- age:> 50 years (glioblastoma); 30-50 years (grade III gliomas); grade II gliomas have a bimodal incidence of 25-44 years and 75-84 years; <18 years (grade I glioma)
- ethnicity: Caucasian, Latino, Asian
- pre-existing diagnosis of low WHO grade astrocytoma (associated risk of malignant transformation grad grade III glioma or glioblastoma)
- the existence of a genetic disease correlated with an increased incidence of gliomas: neurofibromatosis type I and II, tuberous sclerosis, Von Hippel-Lindau disease, Li-Fraumeni syndrome, Turcot syndrome. (3-5)

5. Pathophysiology

Glioblastomas can be classified into primary and secondary tumors. Primary glioblastoma multiforme is responsible for most cases in adults over 50 years, in a percentage of over 60%. It occurs de novo (without the clinically or histopathologically proven existence of a precursor

lesion, with a lower degree of malignancy) and is diagnosed after a short-term clinical course, usually less than 3 months.

Patients under 45 years, develop more frequently a secondary form of glioblastoma multiforme (40% of all cases), which appear by the transformation of a WHO grade II astrocytoma or a WHO grade III anaplastic astrocytoma. The time required for this progression from a low degree to a high degree of malignancy varies considerably, from less than 1 year to more than 10 years, with an estimated average interval of 4-5 years. Increasing evidence suggests that primary and secondary forms of glioblastoma multiforme are different entities, developing on distinct genetic pathways, affecting patients at different ages and responding variably to current therapies.

Of all astrocytic neoplasms, glioblastoma contains the largest number of genetic mutations, resulted, in most cases, from successive, cummulative mutations. (6)

5.1. Genetic abnormalities

From a genetic point of view, primary and secondary glioblastomas overlap very little, the concept of distinct genetic pathways resulting in a common phenotype with general approval in the last decade (Figure 3). The many mutations that can occur must be correlated with the associated prognosis, depending on the frequency of the mutation and the phenotypic changes induced. (7,8)

5.2. Angiogenesis and tumor invasion

Malignant gliomas are among the most vascularized human tumors and are characterized at the same time as being the most invasive of the brain parenchyma. Although angiogenesis and invasiveness are complex processes involving a number of steps, the two largely share common regulatory mechanisms. These regulations depend on the collaboration between growth factors, integrins and proteinases. Many of the pathways described above can initiate the process of angiogenesis, invasion, and tumor growth, and in most cases RPTKs (Receptor Protein Tyrosine Kinase) are involved. Most likely, in the extremely aberrant environment of glioblastoma, there are many pathways activated in addition to the redundant messages from RPTKs

that reach the nuclei of tumor cells. This redundancy may explain why tumor growth in glioblastoma is not stopped by inhibiting a single pathway. The process of angiogenesis, a key factor in glioblastomas, depends strictly on the balance between tumor-stimulating factors (VEGF, PDGF, FGFs and angiopoietin) and inhibitory factors. (9,10)

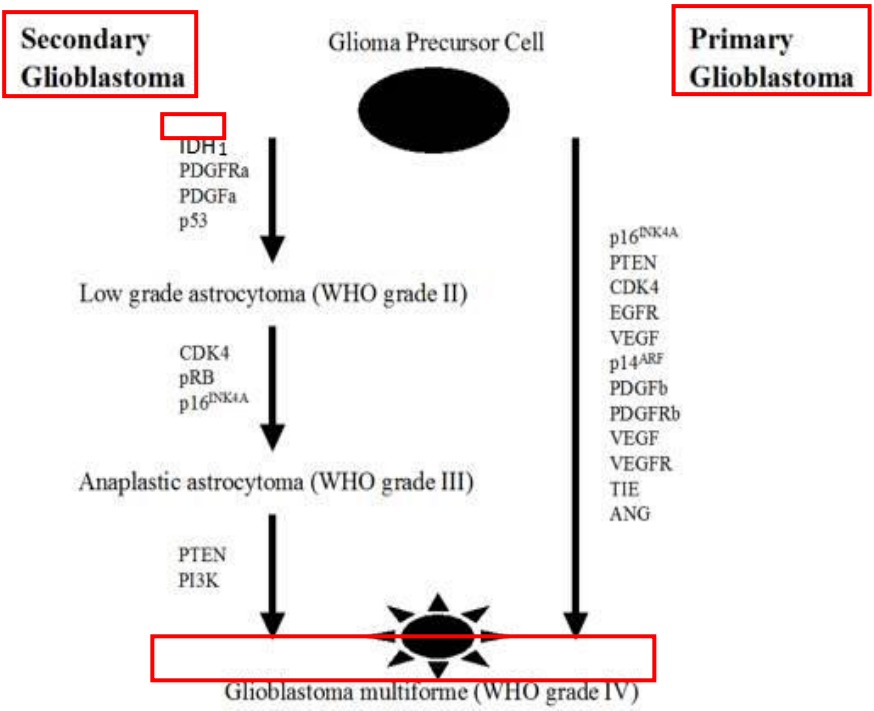


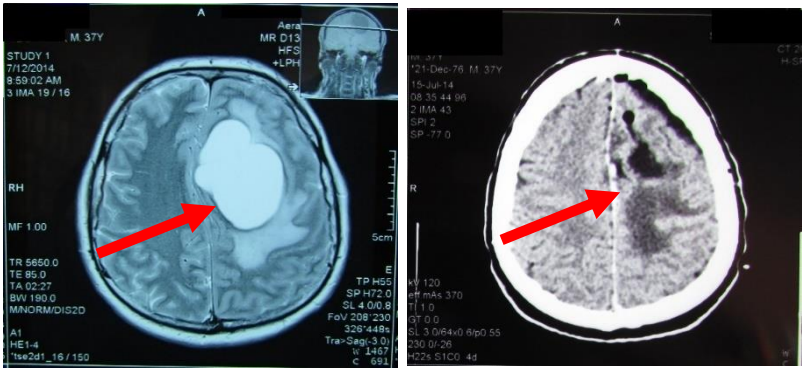
Figure 4. Glioblastoma`s precursor genetic mutations
(Image source: modified after (9))

6. Tumor location

Grade I astrocytomas are benign astrocytomas, often cystic, non-infiltrative and by location can be:

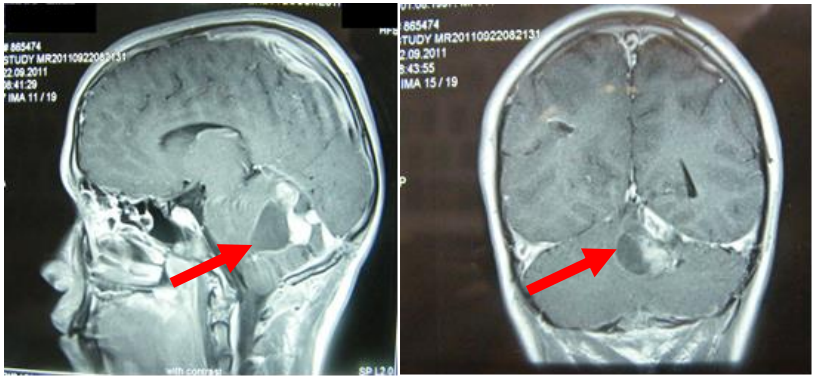
- supratentorial, common in adults, located in the cerebral hemispheres, more frequently the frontal, temporal, parietal lobe. (Figure 5 a and b)

- subtentorial, common in children, predominantly in the cerebellar hemispheres, often cystic (Figure 6 a and b).



a – preoperatively b – post-operatively

Figure 5. Cystic tumor (grade I cystic astrocytoma) left frontal - a and b (Image source: Modified after (11))



a *b*

Figure 6. Cystic tumor vermis ventricle IV.
a-sagittal image; b- front plan image
Image source: Modified after (11)

Grade II astrocytomas are frequently supratentorial in adults and subtentorial in children, often have a cystic component and are generally minimally infiltrative. (12)

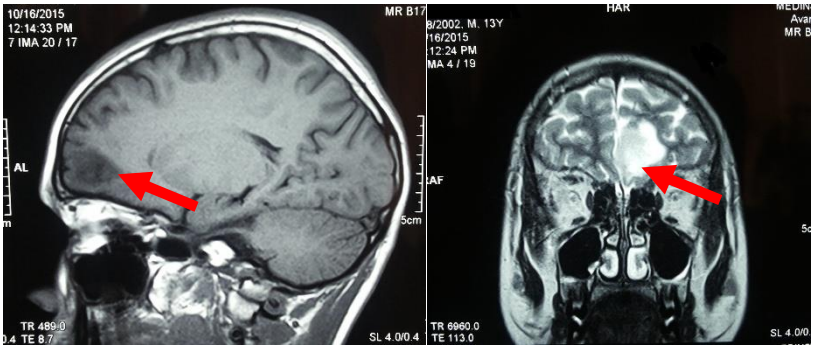


Figure 5. MRI: Sagittal and frontal section; Infiltrative tumor, left frontal-basal, grade II astrocytoma
(Image source: Modified after 13)

Grade III astrocytoma (anaplastic astrocytoma) has the same locations as glioblastoma, the difference on MRI is the appearance of areas of necrosis in the case of glioblastoma.
Grade IV astrocytoma (Gliblastoma Multiform) or glioblastoma, is common in adults (in the cerebral hemispheres) and is extremely aggressive with increased recurrence capacity. The tumor is the predominant site in the white matter of the cerebral hemispheres, secondarily infiltrating the adjacent white matter (Figure 6).

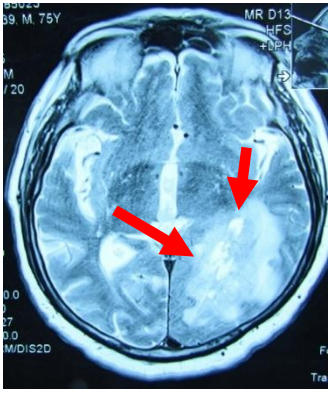


Figure 6. MRI: Giant left temporo-occipital glioblastoma
(Image source: Modified after (14))

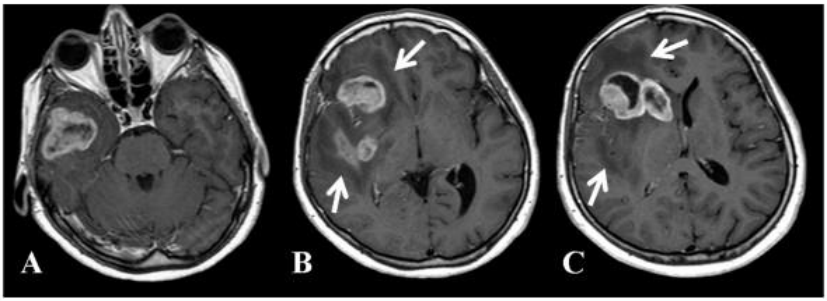


Figure 7. Multiform glioblastoma. A. temporal zone; B. insular lobe, posterior putamen; C. the head of the caudate nucleus. Arrows: the area of perilesional edema.
(Personal collection of Prof. Dr. A.V. Ciurea)

The tumor infiltrates adjacent brain structures: adjacent cortex, basal ganglia, contralateral hemisphere, cerebral peduncles. By infiltrating the corpus callosum to the contralateral hemisphere, the appearance of "butterfly glioblastoma" is created (figure 8).

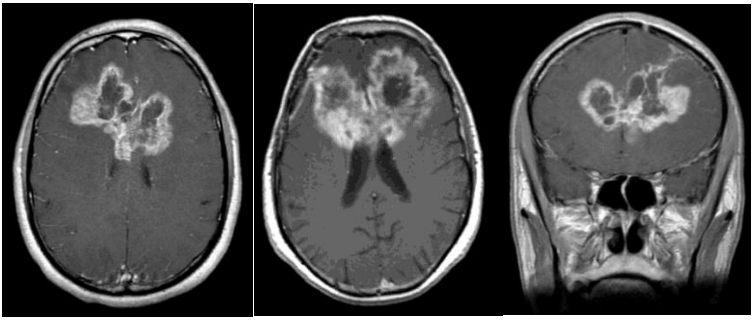


Figure 8. MRI: Butterfly glioblastoma.
(Personal collection of Prof. Dr. A.V. Ciurea)

7. Clinical aspects

The clinical history of the disease is usually short in the case of glioblastoma (less than 3 months in more than 50% of cases), if the neoplasm did not develop from a diffuse WHO grade II astrocytoma or from an anaplastic astrocytoma - secondary glioblastoma, in which case the evolution is slower. In over 50% of cases, the short course of primary

glioblastoma is explained by the rapid development of intracranial hypertension, by compression and infiltration of surrounding brain tissue. The clinical symptomatology of multiform glioblastomas is similar to that of diffuse anaplastic astrocytomas, more frequently accompanied by focal neurological deficit with sudden and rapid onset.

Diffuse grade II astrocytomas and anaplastic astrocytomas infiltrate intact brain tissue without destroying it, compared to glioblastoma, which in addition to the mass effect also produces brain tissue destruction, the clinical effect being focal neurological deficit. This deficiency produces different symptoms, depending on the location of the lesion: frontal lobe - behavioral disorders, personality disorders, contralateral hemiparesis, temporal lobe - coordination disorders, speech and memory disorders, parietal lobe - sensitivity disorders - more common in the case right hemisphere, motor deficit for precise actions, especially in those involving writing skills, occipital lobe - visual hallucinations and visual deficits; cortical hemianopsia, cerebellum - coordination and balance disorders. In the case of the glioblastoma being located in the brainstem, the symptoms will be dominated by paralysis in the cranial nerves by damaging their nuclei (with dysphagia, trigeminal sensory and motor deficits, peripheral facial paralysis), hemifacial spasm, oculomotor disorders, intracerebral hypertension cause by occlusion of Sylvius aqueduct) but pyramidal signs, hemiparesis, ataxia, sensory deficit may also appear. The most common reason for presenting to the doctor is the progressively installed motor deficit, generally translated as muscle deficit.

In 30-50% of cases progressive unilateral hemiparesis translates into a typical lesion of the frontal or temporal lobes or in the thalamic regions. Sudden hemiplegia or a rapidly altered state of consciousness can mimic a stroke, being caused by intratumoral hemorrhage. Often after an epileptic manifestation with nonspecific neurological symptoms, patients have headaches and personality disorders, and the specific signs of intracranial hypertension quickly become evident: headache, vomiting, visual disturbances, papillary edema, cranial nerve III or VI paresis.

Epileptic seizures can be partial, simple, complex or generalized, representing a common manifestation in small tumors of the

frontoparietal region (simple motor or partial sensory seizures) or temporal lobe (partial simple or complex seizures).

Headache, the most common symptom, can vary in intensity and presentation, being more frequent and more severe in the morning or immediately after waking up. Acute cerebral hemorrhage may indicate the clinical onset of a glioblastoma multiforme but it occurs in rare cases. It depends on the synthesis of VEGF, which plays an important role in angiogenesis. The symptoms that appear in patients with a longer survival time are multiple, their diversity is induced by the lack of reversibility of the lesions, by the therapies used or by the extension of the pathology:

- cognitive disorders
- neurological deficits induced by irradiation necrosis
- communicating hydrocephalus
- cranial neuropathies, occasional
- polyradiculopathy due to leptomeningeal extension.

Performance scores

The Karnofsky Performance Score (KPS), calculated on patient presentation, was described in 1949 by Dr. David A. Karnofsky, along with Dr. Joseph H. Burchenal, and presents a scale from 100 to 0, where 100 = healthy patient and 0 = deceased patient. The score was described at 10 percentage point intervals:

- 100% - no signs of disease;
- 90% - patient capable of normal activity, with few symptoms or signs of disease;
- 80% - patient with possible normal activity, with some difficulties present, with some signs or symptoms present;
- 70% - patient able to take care of himself, incapable of normal activity or work;
- 60% - patient who needs a certain degree of help, able to take care of most personal needs;
- 50% - patient in need of frequent medical care;
- 40% - disabled patient, requires specialized care;

- 30% - severely disabled patient, hospitalization indicated but there is no risk of death;
- 20% - urgent hospitalization required, patient with indication for treatment or measures to support vital functions;
- 10% - dying patient, rapidly progressive fatal pathological processes;
- 0% - deceased patient.

The ECOG (Eastern Cooperative Oncology Group) score was published in 1982 by Oken et al.45, and is also known as the WHO or Zubrod score, after Dr. C. Gordon Zubrod, an American oncologist. The WHO score ranges from 0 to 5, 0 signifying the lack of symptomatology and 5 the death of the patient.

• 0 - Asymptomatic; active patient, who can perform all activities prior to the disease, without restrictions;

• 1 - Symptomatic but able to perform light or sedentary activities; restricted from performing strenuous physical activity;

• 2 - Symptomatic, <50% in bed during the day; able to take care of himself but unable to work;

• 3 - Symptomatic,> 50% in bed or armchair, capable of limited personal care;

• 4 - Completely bed-limited patient, completely disabled; he cannot take care of himself;

• 5 - Death.

The equivalence between the Karnofsky score and the ECOG / WHO / Zubord score was validated in a wide range of patients (15) :

- WHO score 0 = Karnofsky 100; 90-100;
- WHO score 1 = Karnofsky 80-90; 70-80;
- WHO score 2 = Karnofsky 60-70; 50-60;
- WHO score 3 = Karnofsky 40-50; 30-40;
- WHO score 4 = Karnofsky 20-30; 10-20;
- WHO score 5 = Karnofsky 0.

8. Histopathological aspects

The histological classification of a glial tumor as an astrocytic tumor depends on the recognition of areas with neoplastic cells that have astrocyte characters and express products of genes found predominantly in these cells. Diffuse astrocytomas, WHO grade II, develop preferentially in the cerebral hemispheres, macroscopically being poorly defined lesions, with moderate cellularity and diffuse infiltration into the cerebral parenchyma but without its destruction.

Unlike diffuse astrocytomas, anaplastic astrocytomas, also located more frequently in the cerebral hemispheres, are characterized by signs of focal or diffuse anaplasia: cellular atypia, hypercellularity, moderate mitotic activity. Glioblastoma, with a preferential supratentorial location, is most often represented by a necrotic mass, with intratumoral hemorrhages and an area bordered by tumor tissue, hypercellular. The histopathology of glioblastoma multiforme is extremely varied, a fact suggested by the very name of this tumor. Glioblastoma consists of pleomorphic astrocytes, poorly differentiated, with marked nuclear atypia and increased mitotic activity. Necrosis is an essential element in the diagnosis of glioblastoma, frequently accompanied by sustained microvascular proliferation. Most glioblastomas are strictly intraparenchymal, with a white epicenter, but can sometimes spread and come into contact with leptomeninges or dura mater. (16)

9. Neuroimaging

Imaging diagnostic methods for glial tumors are generally CT and MRI, as well as spectroscopic magnetic resonance imaging is important to determine the level of metabolic activity within the tumor process - suspicion of a malignant or benign tumor. The contrast agent can better highlight the tumor edges.

Grade I astrocytomas (so astrocytomas that do not fall into the infiltrating category) cannot be staged neuroimaging.

WHO grade	Typical radiographic findings	Location
Diffuse astrocytoma (WHO grade II)	CT: low density MRI: abnormal signal on T2WI No enhancement with little or no mass effect	Temporal, posterior, frontal and anterior parietal lobes
Anaplastic astrocytoma (WHO grade III)	Complex enhancement	
Glioblastoma, IDH wildtype (WHO grade IV)	Central necrosis with ring enhancement	Temporal> parietal> frontal> occipital
Glioblastoma, IDH wildtype (WHO grade IV)	Solid enhancement	Frontal lobe: predilection

Figure 9. Grading of gliomas on CT or MRI (17)

In computed tomography, the glioblastoma has an irregular shape, with a circular peripheral area ring-like, which captures intense contrast and a hypodense central area, which represents necrosis. Thus, the inhomogeneous image of an infiltrative, contoured or completely irregular tumor process is observed, which presents in the periphery an iodophilic contrast ring that surrounds a central necrotic hypodense area. Glioblastoma multiform also has a large area of edema, with a hypodense appearance.

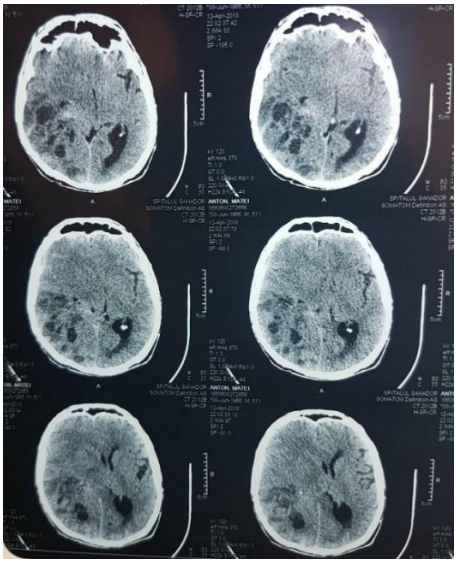


Figure 10. CT native: Glioblastoma - right parietooccipital with predominantly hypodense inhomogeneous structure with multiple cystic areas up to 2 cm and hyperdense internal areas. Mass effect on the right LV with displacement to the left of the midline structures.
(personal collection of Prof. Dr. A.V. Ciurea)

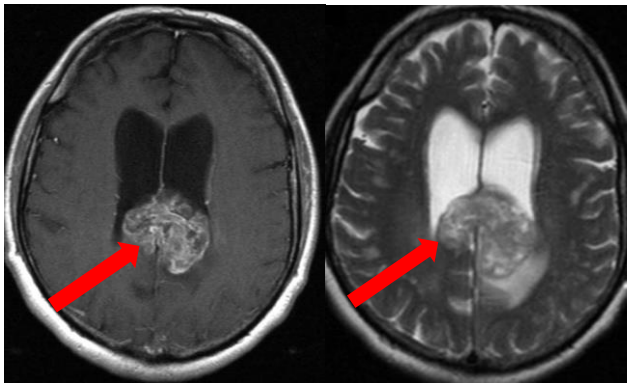


Figure 11. Butterfly glioblastoma. Left: RM, axial T1 contrast agent. Right: RM, axial T2
(Personal collection of Prof. Dr. A.V. Ciurea)

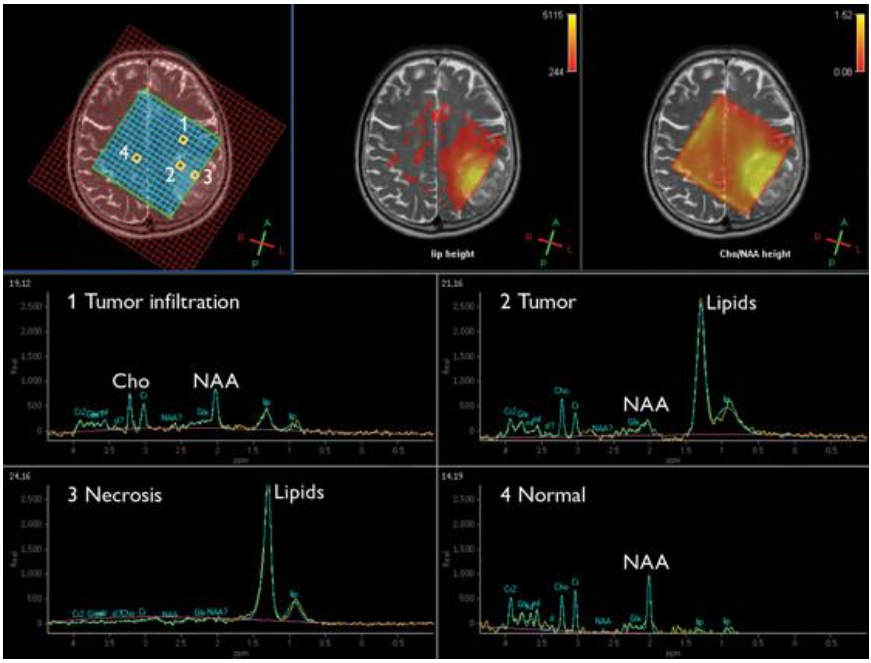


Figure 12. MRI glioblastoma spectroscopy (18)
(Personal collection of Prof. Dr. A.V. Ciurea)

Tractography is a non-invasive imaging technique that allows the specific definition of white matter tracts and the relationship between tumor mass and the trajectory of these tracts.

Three particular aspects were identified by tractography:

- interruption - especially in the case of glioblastoma that affects the corpus callosum;
- displacement - in the affected hemisphere can be observed the displacement of the corticospinal tracts, with the preservation of the axons;
- infiltration.

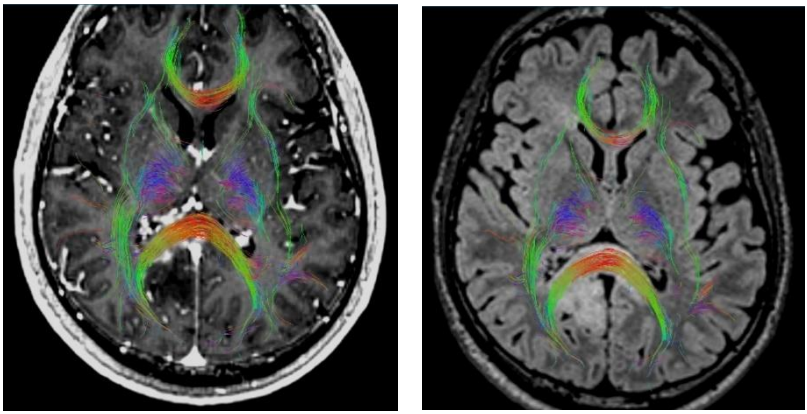


Figure 13. Tractography image and movement and infiltration of fibers by glioblastoma
(Image source: modified after (18))

10. Differential diagnosis

The differential diagnosis of infiltrative glial tumors is made with:

❖ Other brain tumors: meningiomas, astrocytomas, oligodendrogliomas; in favor of glioblastoma: the diagnosis is favored by the irregular shape of the tumor mass, by the central necrosis but also by the peritumoral edema and the mass effect.

❖ Metastases: should be considered and this diagnosis is unlikely, however, given the age of the patient and the lack of a history of primary tumor.

❖ Cerebral abscess: frequently identified as having a thin, regular ring with intense contrast, which circumscribes a central cavity.

❖ Primary lymphoma in the CNS: a rare form of non-Hodgkin's lymphoma, may occasionally have a butterfly-like appearance, when it includes the corpus callosum.

❖ Multiple sclerosis lesions: rare; The borderline form of multiple sclerosis, Balo concentric sclerosis, can be a differential diagnosis with glioblastoma that is difficult to make, due to the similarities between the clinical presentations and the radiological aspects highlighted.

❖ Progressive multifocal leukoencephalopathy: caused by JC virus infection, which causes axonal demyelination.

- ❖ Cavernous malformations;
- ❖ Intracranial hemorrhage;
- ❖ Radiation necrosis;
- ❖ Toxoplasmosis
- ❖ Glioblastoma headache must be differentiated from other causes like: hypertension, migraine;
- ❖ Epileptic manifestations of glioblastoma must be differentiated from other causes: epilepsy, drug side effects, alcohol withdrawal syndrome, hypoglycemia.

The two most common entities are: **carcinomatous metastasis** and **cerebral lymphoma**. (19)

11. Treatment methods

The treatment of infiltrative glial tumors is complex, multimodal, applied to try to stop the tumor evolution, prolong survival and ensure an acceptable quality of life. Treatment of this condition is very difficult due to the resistance of tumor cells to chemotherapy or other conventional therapies and the susceptibility of brain tissue to be affected during treatment. Another impediment in the therapeutic approach is the inability of some drugs to cross the blood-brain barrier.

The standard treatment for infiltrative glial tumors in adults (glioma grade II, III, IV) is currently surgical, followed by conventional external radiation therapy or brachytherapy and chemotherapy.

The objectives of this multimodal treatment are:

1. Confirmation of the diagnosis;
2. Relief of symptoms;
3. Removal of cells with treatment resistance potential before their multiplication;
4. Reducing the number of malignant cells;
5. Sensitization of tumor cells by oxygenation;
6. Reducing the harmful effect of products released by tumor cells and their effect on the surrounding noble tissue.

Surgery allows:

- establishing the diagnosis by stereotactic biopsy or biopsy by open surgery;

- surgical resection of a tumor mass without worsening the patient's symptoms, relieving the symptoms of the mass effect = debulking;

- improving survival and quality of life in 95% of cases.

Radiotherapy - affects the DNA helix through ionizing radiation, producing electrons and free radicals.

Chemotherapy - destroys tumor DNA or inhibits its replication.

The most important part of managing patients diagnosed with glioblastoma is patient support, compassion, and improving their quality of life as much as possible.

Continuous treatment for the recovery and preservation of the patient's ability to perform minimal or complex activities must be extended physically, occupationally and psychologically, through physiokinetotherapy, speech therapy and psychotherapy. The patient should be encouraged and educated about the diagnosed tumor pathology. Positive attitude towards the disease, social and professional reintegration as soon as possible, maintaining a healthy diet and activity, even minimal, are important aspects of supportive treatment. The patient and his family should be instructed to keep a chronological and up-to-date record of all medicines used, to be cautious of any signs of infection or bleeding in order to seek medical advice as soon as possible.

11.1. Surgical treatment

Surgery on nervous system tumors must meet three objectives:

1. specification of the histopathological diagnosis of the tumor variety,
2. decompressive treatment
3. the widest possible ablation of the tumor mass. Immunotherapy and chemotherapy are all the more effective as they target a small tumor population in a state of active metabolic exchange.

Surgical treatment must maintain a balance between increasing long-term survival after extensive tumor resections and significantly affecting patients' quality of life.

Surgical excision, although it cannot cure glioblastoma, brings many advantages when performed as completely as possible:

• Reduces the frequency of hemorrhages in the tumor bed, by ablation of neoformation vessels;

• Decreases the mass effect;

• Facilitates adjuvant therapies, both the conditions in which it will be administered and the possibility; local administration of radiotherapy with its variants and chemotherapy;

• Improves the neurological status of patients, prolonging survival and maintaining quality of life.

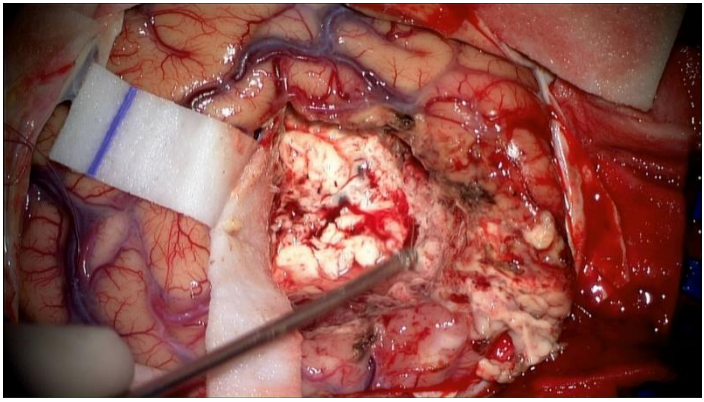


Figure 14. Intraoperative image - Glioblastoma;
(Personal collection of Prof. Dr. A.V. Ciurea)

Radical reduction of tumor mass leads to rapid decompression of normal brain tissue that suffers due to the mass effect and cause of the extensive peritumoral edema. Due to the cytoreduction in the tumor bed, the probability of an optimal response to radiotherapy and / or chemotherapy thus increases, also giving a possible decrease of the disease progression. Due to the infiltrative elements of glioblastoma and the involvement of eloquent areas, the resection is often partial. This leads to faster tumor recurrence and thus a poor prognosis.

Radical surgical resection has many advantages but the arguments for and against an intervention as complete as possible must be taken into account.

PRO arguments for radical resection	Arguments AGAINST radical resection
Decreased intracranial hypertension	The tendency of glioblastoma to invasiveness and tumor infiltration; the impossibility of a total resection
Reversibility of neurological deficit	Potential for tumor cell dissemination during surgery
Cytoreduction - removal of cells resistant to adjuvant therapies, located in the tumor center. (poor vascularity and low O2 pressure)	Possibility of developing postoperative complications or new neurological deficits - "primum non nocere"
Elimination of epileptic seizures	Existence of multifocal glioblastoma tumor variants
Prolongs survival and increases tumor susceptibility to radio and chemotherapy, enhancing both brachytherapy and hyperthermia and immunotherapy	
Provides accurate diagnosis, reducing diagnostic error by biopsying	

Figure 15. Advantages and disadvantages of radical resection (20)

Surgery must be rigorously planned: approach, stereotactic craniotomy in case of inaccurately determined tumors or deep lesions or at the level of eloquent areas. The degree of resection can be improved by performing an image-guided intervention, by functional MRI, by using electrophysiological mapping, and neuronavigation, to

delimit the eloquent areas and the relationship of the tumor mass with important cortical regions.

Another procedure that helps the neurosurgeon perform a resection with low tumor residual volume is the use of 5-aminolevulinic acid. This substance causes the synthesis and accumulation of fluorescent porphyrins (protoporphyrin IX) in neoplastic tissues, including gliomas of increased malignancy. (21)

Stereotactic biopsy can be considered in the following situations:

1. The tumor is located in a central, deep area, poorly delimited by CT or MRI or located in a brain area of great importance;

2. The tumor is small, less than 2 cm;

3. The patient has significant comorbidities and cannot undergo open surgery under general anesthesia; Karnofsky score <70;

4. Patient with minimal neurological deficit;

5. To differentiate between glioblastoma and another tumor, which could be successfully treated by irradiation- for example: lymphoma, both having similar neuroimaging;

6. To administer as accurately as possible the following: brachytherapy, interstitial hyperthermia, interstitial phototherapy, stereotactic radiosurgery;

7. In cases requiring repeated tissue biopsies.

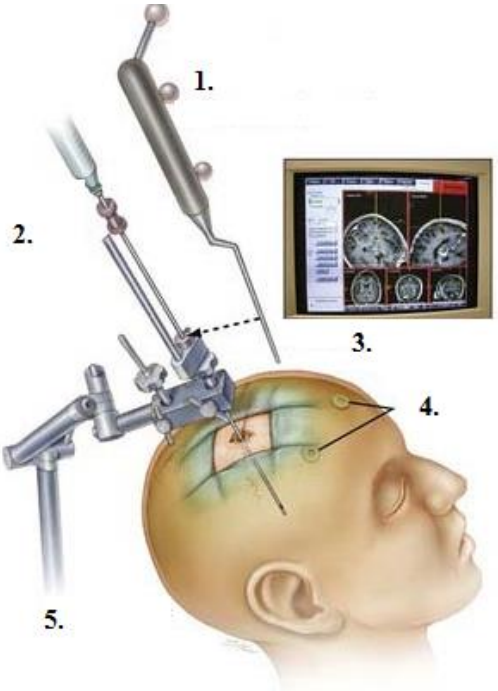


Figure 16. Stereotactic biopsy system using neuronavigation
1. Stereotactic marker for navigation
2. Cannula for biopsy
3. Real-time neuronavigation
4. Reference points for neuronavigation
5. Stereotactic biopsy device attached to a Mayfield system
(Image source: Modified after (22))

11.2. Radiotherapy

Radiation therapy can be given in addition to surgery or chemotherapy, prolonging the survival of patients with glioblastoma, compared to strictly surgical treatment. It can reduce tumor size to 10^7 cells by inducing changes in the helix of DNA through electrons and free radicals. Thus, they try to destroy the cells infiltrated at a distance from the tumor bed, but also to prolong the period of recurrence.

The invasiveness of glioblastoma-type brain tumors makes total resection impossible. Extended resections are often associated with reduced neurological function, a factor that reduces the quality of life of these patients. The application of adequate irradiation doses is hampered by the presence of organs at risk. (e.g.: optic nerve, optic chiasm, brainstem and even lens). In this case, targeted irradiation techniques such as conformational irradiation or IMRT (modular intensity radiotherapy) technique were developed.

There are several techniques, perfected over time, for irradiating glioblastomas:

- ✓ External beam radiation
- ✓ Stereotactic brachytherapy - involves the use of stereotaxic techniques for the precise placement of catheters containing radioactive isotopes (^{125}I, ^{252}Californium) inside the brain tumor without having adverse side effects on noble tissue
- ✓ Gliasite Radiation Therapy System -designed for the distribution of intracavitary radiotherapy after surgical resection.
- ✓ Thermotherapy - heat administration at 45°C for one hour, through microwave antennas at 915 or 2450 MhZ.

The technique is used in the treatment of tumors under <3 cm, radiologically well-defined lesions, through a single high dose of ionizing radiation, stereotactically directed to the tumor bed in bundles. Radiosurgery is noninvasive allowing the treatment of patients with tumors located in surgically inaccessible areas or in eloquent brain areas and patients with significant comorbidities.

Radiosurgery uses beams of ionizing radiation, in large doses, directed to obtain in a single session a radiobiological effect at the level of a predetermined target volume by:

- ❖ Cyclotron with heavy particles - protons;
- ❖ Linear electron accelerator - X-rays with 4-18 MV;
- ❖ Gamma Knife: 201 sources of Co^{60}- gamma radiation, used together with radiosensitizers: gadolinium texaphyrin, RSR 13 (frequently used in tumor recurrences).

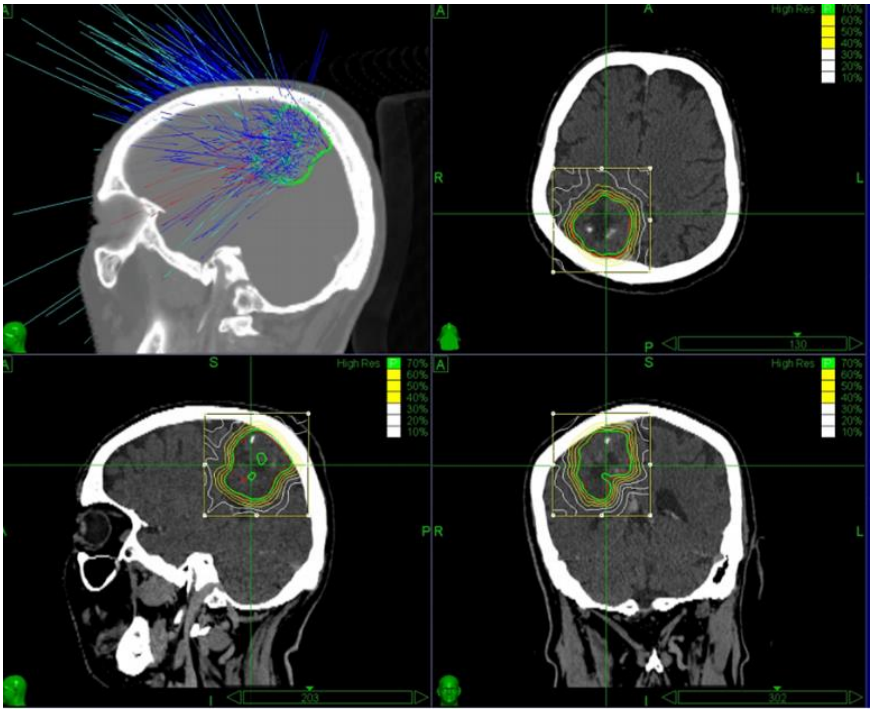


Figure 17. Glioblastoma in the right parietal area treated by stereotactic radiosurgery
(Image source: Modified from (22))

11.3. Chemotherapy

The indications for chemotherapy are: post-surgical treatment, concomitant or post-radiotherapy. Chemotherapy also helps prevent recurrences and CSF dissemination, but the response to chemotherapy in intracerebral tumors is structurally limited by the blood-brain barrier. The following cytotoxic agents are used in the treatment of glioblastoma with chemotherapeutic agents:

1. Temozolomide (TMZ);
2. Nitrozuree (BCNU-carmustine);
3. PCV- Procarbazine +CCNU(lomustine)+ vincristine;

In combination with cytotoxic agents, cytostatic agents may be used:

1. **Cis-retinoic acid**- A synthetic analogue of vitamin A, 13-cis retinoic acid (isotretinoin) binds to retinoic acid receptors and retinoic X receptors, members of the nuclear steroid receptor family.
2. **Thalidomide**- immunosuppressant with main indication as first-line treatment in multiple myeloma.
3. **Tamoxifen**- selective estrogen receptor modulator, acts only on cells that have this type of receptor. It is most used in breast cancer.
4. **Cyclooxygenase 2 inhibitors (COX 2)**– for example: Celecoxib, which has antiproliferative effects by losing the activity of cyclin-dependent kinases, regulators of cell proliferation. [24]

11.4. Immunomodulatory treatment

Optimal therapeutic management of glioblastoma patients is a challenging and difficult goal to achieve. Despite the promising results of the introduction of temozolomide chemotherapy into the treatment of glioblastoma, the prognosis of patients diagnosed with this tumor remained bleak. The new strategies for the treatment of glioblastoma, currently under investigation, are designed to have a more specific approach to the mechanisms of tumorigenesis and angiogenesis at the tumor level.

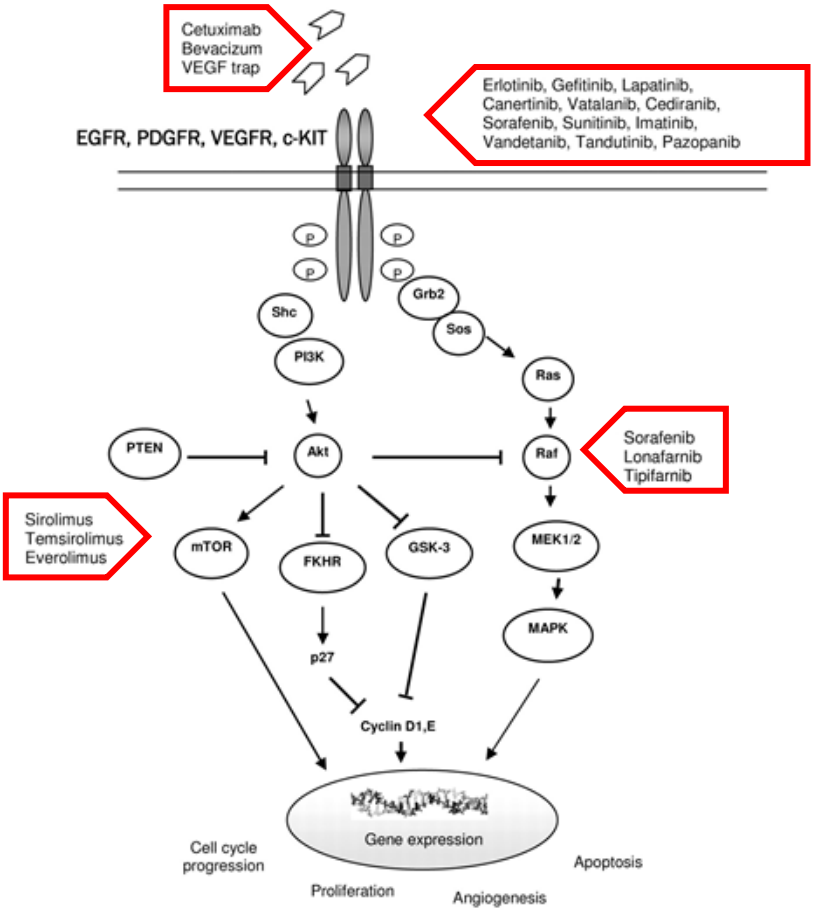


Figure 18. Schematic representation of the main oncogenic signaling pathways and the place of action of current molecular therapies. PLC= phospholipase C; PHc= protein kinase C; P13K=phosfatidillinozitol 3'- Linase; PTEN= phosphatidyl and tensine homolog, Akt= V-akt murine thmoma viral oncogene homolog; mTor= mammalian- target of rapamycin.
(Image source: Modified after (25,26))

11.5. Symptomatic treatment

1. Anticonvulsants - AAN (American Academy of Neurology) practice guidelines do not recommend routine prophylactic administration of antiepileptic drugs in newly diagnosed brain tumors. Postoperatively, discontinuation of antiepileptics is recommended after the first week if the patient does not have any seizures. You can use: levetiracetam (1000-3000 mg / day), phenytoin (15mg / kg loading, 5mg / Kg / day maintenance), carbamazepine (600-1000 mg / day) or phenobarbital (90-150 mg / day).

Levetiracetam is mainly used in the treatment of partial or myoclonic seizures, but it is also indicated in generalized tonic-clonic primary seizures. The dose should be reduced in patients with kidney failure and the side effects of levetiracetam include: drowsiness, asthenia, mild leukopenia, behavioral changes such as anxiety, emotional lability, depression, psychosis. The frequency of seizures may increase when treatment is stopped abruptly.

Phenytoin acts on sodium channels, blocking them and thus preventing repetitive electrical discharges. It is a first-line drug in the treatment of partial or generalized tonic-clonic seizures. Requires monitoring by blood tests both at the beginning of administration and at 1-month intervals because it causes blood dyscrasias. Contraindications to phenytoin are sinoatrial block, grade II, atrioventricular blocks, sinus bradycardia and Adams-Stokes syndrome. Rapid IV injection can cause cardiac arrest by enlarging the QRS complex.

Carbamazepine has a common mechanism of action with that of phenytoin, blocking repetitive neuronal discharges through sodium channels. Represents a first-line therapeutic agent in case of partial or tonic-clonic seizures, but hemogram, ionogram and intraocular pressure must be monitored throughout the treatment period.

2. Corticosteroids – reduce peritumoral vasogenic edema, decrease the mass effect and decrease intracranial pressure, relieving headache and lateralization symptoms. Corticosteroids are also effective in treating cerebral gliomas due to the reduction of brain glucose metabolism at the tumor level.

Dexamethasone is the most widely used corticosteroid, acting by decreasing vascular permeability and decreasing CSF production. The initial dose is about 16 mg / day, but can be adjusted later for optimal symptom control. Among the drug interactions, co-administration of dexamethasone with barbiturates, phenytoin or rifampicin should be specified, which may lead to diminished therapeutic effects. Dexamethasone also interacts with salicylates and immunization vaccines, reducing their effect. Contraindications to dexamethasone are active bacterial and fungal infections. Dexamethasone increases the risk of complications: severe infections, adrenal insufficiency when stopping administration, hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer, hypokalemia, osteoporosis, euphoria, psychosis. (27)

12. Prognostic

Despite numerous clinical studies conducted to better understand the pathophysiology, evolution, therapeutic response of GB, the attempt to find a way to individually predict the clinical course of this disease has been left without a reliable scientific answer.

GB are among the most malignant neoplasms, with an average survival, despite an optimal treatment of less than 1 year.

There is a prognostic scale for patients diagnosed and operated for gliomas with a high degree of malignancy, in relation to the histological type and the Karnofsky gradation of the neurological deficit. A one-year survival rate of 32% was found for all patients with these malignancies of brain tumors. The evolution of patients with malignant gliomas after optimal treatment was assessed according to the size of the tumor remaining at the paraclinical control examinations, the need for corticotherapy and the evidence of a new lesion, that: healing, partial response, minor response, absence of remission or progression of tumor lesion.

The average survival time from the time of diagnosis, without treatment, is about 3 months. With optimal treatment this period can increase up to 1-2 years of survival. Less than 2% of patients survive more than 3 months from the time of diagnosis and are considered LTS-Long

Term Survivors. Death usually occurs due to cerebral edema or intracerebral hypertension.

Patient survival depends on a number of clinical parameters: young adults, Karnofsky performance score with a high presentation value, radiotherapy and chemotherapy correlate with a better prognosis. Clinical evidence has also shown that extended resection promotes longer-term survival, while the inability to perform a resection due to the location of the tumor mass (eg brainstem) predicts an unfavorable prognosis. (28,29,30)

Prognostic factors:

- The degree of malignancy of the relapsed tumor;
- The time interval from the previous intervention until the appearance of the tumor recurrence;
- The degree of resection of the tumor at the first intervention;
- Location and extension of the intracerebral lesion;
- Morphological characteristics of the lesion;
- Patient age and Karnofsky score.

Favorable prognostic factors:

- Low degree of tumor anaplasia;
- MGMT gene methylation;
- Young patients <50 years;
- Karnofsky score increased at presentation> 70;
- Quasi-total resection of the lesion at the first intervention;
- Administering a complementary treatment to multimodal and aggressive surgery;
- Long time interval between relapses;
- Recurrence located in non-eloquent areas;
- Good biological condition after chemo and radiotherapy.

Unfavorable prognostic factors:

- High degree of tumor anaplasia, with numerous nuclear atypia and sustained mitotic activity;
- Presence of necrosis at the tumor level;
- Advanced age of patients;
- Low Karnofsky score on presentation <70;
- Incomplete tumor resection, only to remove the mass effect; performing a biopsy exclusively;

➢ Occurrence of tumor recurrences shortly postoperatively or during complementary treatment;

➢ Tumor localization in eloquent areas, in areas that increase the difficulty or contraindicate a complete resection (for example: brainstem).

Abbreviations:

GB= glioblastoma; **GBM**= glioblastoma multiforme; **PLC**= phospholipase C; **PHc**= protein kinase C; **RPTKs**= Receptor Protein Tyrosine Kinase; **LV**= lateral ventricle; **WHO**= World Health Organization; **COX 2**= Cyclooxygenase 2 inhibitors; **IDH1**= isocitrate dehydrogenase1; **NOS**= not otherwise specified; **P13K**=phosfatidillinozitol 3-Linase; **PTEN**= phosphatidyl and tensine homolog; **Akt**= V-akt murine thmoma viral oncogene homolog; **mTor**= mammalian- target of rapamycin

References:

1. Banan R, Hartmann C. The new WHO 2016 classification of brain tumors-what neurosurgeons need to know. Acta Neurochir (Wien). 2017 Mar;159(3):403-418
2. Ostrom Q.T., Gittleman H., Xu J., Kromer C., Wolinsky Y., Kruchko C, Barnholtz-Sloan J. S.; CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2009–2013, *Neuro-Oncology*, Volume 18, Issue suppl_5, 1 2016 Oct;1–75
3. Huncharek M, Kupelnik B, Wheeler L. Dietry cured meat and the risk of adult glioma: a metanalysis of nine observational studies. J Environ Pahol Txicol Oncol. 2003; 22 (2): 129-37
4. Johnson DR, Fogh SE, Giannini C, Kaufmann TJ, Raghunathan A, Theodosopoulos PV, Clarke JL. Case-based review: Newly diagnosed glioblastoma. Neuro-Oncology Practice. 2015;2:106–121.
5. Carlberg M, Hardell L. Evaluation of Mobile Phone and Cordless Phone Use and Glioma Risk Using the Bradford Hill Viewpoints from 1965 on Association or Causation. Biomed Res Int. 2017; 21-29.
6. Onciul R. Aspecte actuale in tratament glioblastomului cerebral multimodal., UMF Carol Davila, 2018; 13-14

7. Rich JN, Hans C, Jones B Gene expression profiling and genetic markers in glioblastoma survival. Cancer Res. May 15 2015; 65(10):4051-8
8. Kleihues P, Burger PC, Cavenee WK. Glioblastoma. In: WHO Classification: Pathology and genetics of tumors of the nervous system. Ed Lyon France: International Agency for Reasearch on Cancers;2017:16-24
9. Kamnasaran D. Stem cells and models of astrocytomas. Clin Invest Med 2009; 32 (2): E166-E179.
10. Stansky B., De Souza SJ.: Modeling tumor evolutionary dynamic. FrontPhysiol 2012; 3:480
11. Iencean S., Ciurea A.V., Tumori intracraniene în Tratat de Neurochirurgie, Vol. I, Ed. Medicală, București, pg. 388-433, 2010.
12. Kaye A.H., Walker D.G., Low-grade glial neoplasms în Neurological surgery, principles and practice, Hunt Batjer H., Loftus C.M., Lippincott Williams & Wilkins, 2003. 161-178
13. Ciurea A.V., Tratat de Neurochirurgie Vol. 2, Editura Medicală, București, 2011. 78-94
14. Onciul R. Aspecte actuale in tratament glioblastomului cerebral multimodal., UMF Carol Davila, 2018; 26-27
15. Ciurea A.V, Iencean S., Mohan D., Simptomatologia tumorilor intracraniene, în Actualităţi în tumorile intracraniene, Editura Universitară, București, 2011. 114-135
16. Claes A, Idema AJ, Wesseling P. Diffuse glioma growth: a guerilla war. Acta Neuropathol. Nov 2007; 114(5): 443-458
17. Greenberg M.S.Handbook of neurosurgery. Ninth Edition.Thieme. 2020; 36: 622-623
18. Onciul R. Aspecte actuale in tratament glioblastomului cerebral multimodal., UMF Carol Davila, 2018; 43-44
19. Constantinovici A., Ciurea A.V., Ghid practic de neurochirurgie, Ed. Medicală, Bucureşti, 1998.
20. Iencean S., Ciurea A.V., Tumori intracraniene în Tratat de Neurochirurgie, Vol. I, Ed. Medicală, București, pg. 403-451, 2010.
21. Kleinberg LR, Stieber V, Mikkelsen T, Judy K, Weingart J, Barnett G, Olson J, Desideri S, Ye X, Grossman S. Outcome of Adult Brain Tumor Consortium (ABTC) prospective dose-finding trials of I-125 balloon brachytherapy in high-grade gliomas: challenges in clinical trial design and technology development when MRI treatment effect and recurrence appear similar. J Radiat Oncol. 2015 Sep;4(3):235-241.

22. Woodworth GF, McGirt MJ, Samdani A. Frameless image-guided stereotactic brain biopsy procedure: diagnostic yield, surgical morbidity, and comparison with the frame-based technique. J Neurosurg. 2006;104:233-237.
23. Niranjan A, Faramand A, Lunsford LD. Stereotactic Radiosurgery for Low-Grade Gliomas. Prog Neurol Surg. 2019;34:184-190.
24. Yeng L.C., "Strategies of Temozolomide in Future Glioblastoma Treatment." *OncoTargets and therapy* 10 (2017): 265–270.
25. Anderson JC, McFarland BC, Gladson CL. New molecular targets in angiogenic vessels of glioblastoma tumours. Expert Rev Mol Med. 2008 Aug 710-723.
26. Reardon DA, Wen PY, Desjardins A, Batchelor TT, Vredenburgh JJ. Glioblastoma multiforme: an emerging paradigm of anti-VEGF therapy. Expert Opin Biol Ther. 2008 Apr;8(4):541-53.
27. Onciul R. Aspecte actuale in tratament glioblastomului cerebral multimodal., UMF Carol Davila, 2018; 63-64
28. Donato V, Papaleo A, Banelli E. Prognostic implication of clinical and pathologic features in patients with glioblastoma multiforme treated with concomitant radiation plus temozolomide. Tumori. Jun 2007; 93(3):248-256.
29. Cheng JX. Helath-related quality of life in glioma patients in China. BMC Cancer. Jun 2010, 10:305.
30. Ohagaki H, Kleihues P. Population-based studies on incidence, suvival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. J Neuropathol Exp Neurol. Jun 2015; 64(6):479-489.

CRANIOPHARYNGIOMA

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Introduction

Craniopharyngiomas (CP) are rare, benign, extra-axial disembryoplastic tumors that account for <1% of all brain tumors, but are the most common non-glial tumors in children. According to Bunin et al. the frequency of craniopharyngiomas is 1.3 per 1,000,000 people / year.[1] The incidence of these tumors is bimodal with 2 peaks at the age of 5-14 years and in adults at 50-74 years. CP accounts for 9% of all intracranial tumors in children.[2] The survival rate is high, > 85% after treatment, and the multimodal approach is associated with increased survival.[3] Symptoms are determined particularly because of the mass effect and tumor invasion of the optic chiasm, optic tracks, pituitary gland, hypothalamus, third ventricle or even lateral ventricles, cavernous sinous and other cranial nerves. The most frequent combination of the symptoms consists of visual deficits with hormonal abnormalities. Considering the invasive character of the tumor many advocate for subtotal resection coupled with adjuvant therapy, however, we consider that the gross-total resection, when possible, is the best choice for the treatment.

Etiology

The two theories that underlie the formation of CP are the theory of embryonic origin and the metaplastic theory. In metaplastic theory,

CP develops from the embryonic remains of the Rathke pouch or from the vestiges of the craniopharyngeal duct, which supports the appearance of the adamantinomatous type. The metaplastic theory supports the appearance of papillary CP in adenohypophyseal cells. Mutations in the BRAF and CTNNB1 genes involved in cancers also lead to craniopharyngiomas.[4] Papillary CP is located most often in the upper part of sella as a result of squamos metaplasia that seems to form squamous nests by modification of the pituitary upper cells.

A major role in the CP onset is the alteration of Wnt/beta-catenin path which is responsible for cell proliferation, development and migration. Aberant Wnt activation was reported in adamantinomatous type. Additionaly, Axin 2, a target gene activation in adamantinomatous type was over-expressed in cells with beta-catenin accumulation. The modified gene of CTNNB1 is carried out in the exon 3 of the altered cell and is associated with beta-catenin accumulation in cells.[5] BRAF V600E is another mutation encountered in CPPap in 81% of the cases, which may allow the use BRAF-inhibitor therapy for the patients with this type of tumor.[6]

Morfopathology

There are 2 distinct types of craniopharyngiomas: adamantinomatous (CPAd) and papillary (CPPap), the first of which is 9 times more common than the second one. While CPAd has a bimodal incidence in both children and the elderly, the CPPap appears only in children. CP Adamantinomatos is composed of a liquid similar to "car oil", with a solid component and calcifications. This type is composed of cellular nests and trabeculae of epithelium surrounded by gliotic tissue. The squamous epithelium may vary from the classical “palisading” epithelium to a more thin one in cystic areas. Presence of keratin may lead to unknown-body granulous formation.[7]

In contrast, CPPap is mostly solid, better demarcated, consisting of a mature squamous epithelium and pseudopaples that are protruding in the brain tissue. CPPap lacks any of the characteristic of the adamnatinomatous type specifically the stellate cell region and keratine nodules. This type of tumor doesn’t exfoliate large quantities of

epithelial cells into the lumen and they rarely gets calcification. Its "oil" content is less darker than the other type of CP.[8]

While it was considered that the adamantinomatous type could be more invasive and with high reccurence rate than the papillary type. Yet, these hypothesis were not validated so far. The difference between the two types is made on the basis of histological characters but also on the basis of beta-catenin accumulations.[9] According to the data from our series, 53% of them are cystic and 33% have a mixed structure.[10]

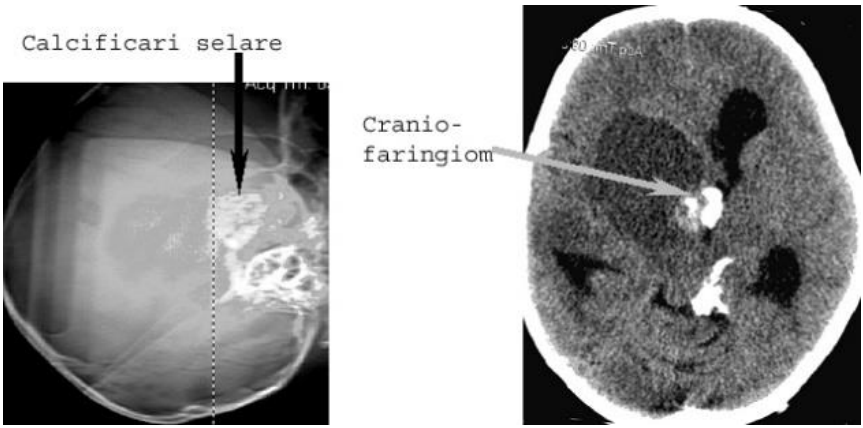

Figure 1: Craniopharyngioma (Radiography and CT – scan)[15]

Clinical features:

The most common clinical aspects are nausea, vomiting, visual disturbances, hormonal disorders, diabetes insipidus, obesity, basal metabolic disorder.

Non-specific symptoms are related to the **increased intracranial pressure** (ICP). ICP usually consists of headaches in 50% of the cases with nausea, vomiting, and meningeal irritation. The most common visual disturbance is temporal hemianopsia because of compression of the optic chiasm.[11] **Hormonal disorders** are caused because of the disturbance of the pituitary-hypothalamic axis. Hormonal status is worsen in the adult patients than in pediatric patients. At least one hormonal deficit is present at the hospital admission associated with Diabetes Insipidus. Among the most frequent hormonal deficits,

growth hormone deficit, gonadotrofin deficits, adrenocorticop hormones deficits and thyroid hormone deficits are the most frequent.

Obesity and hypothalamic disturbance are another aspects of the tumor agressivness. Hypothalamic involvement may lead to alteration of the satiety cicle, metabolic expenditure and sleep dysfunction. It is well known that despite the fact CP are slowly growing and has a high survival rate, the Quality of Life (QoL) for such tumor is dependent on the level of invasiveness at the time of diagnostic. The tumor extension to the hypothalamus was associated in 76% cases with obesity and 96% of severe obesity patients compared to 33% of normal weight survivors.[12]

Visual impairment is associated with tumor extension at the site of the optic chiasm. Of the 80 cases of reported at prechiasmatic site, 24 of them were presenting proeminent prechiasmatic growth.[13] Visual impairment was reported at 50.3% cases from a pediatric cohort at diagnostic. Other significant visual function markers such as visual acuity (41.3%), visual function loss (38.3%), papilledema (25.8%) were present. Strabismus, diplopia and 3rd, 4th and 6th nerve deficits are other signs of CP extensive character in the suprasellar region.[14]

Due to its large size, CP can cause **neurological signs** (pyramidal syndrome, hemiparesis, sensitive syndrome with asterognosis and hemihypoaesthesia).

Epilepsy can manifest either in the form of generalized seizures (compression of the diencephalic formations), or in the form of temporal seizures, or in the form of vegetative epilepsy (violent headache, dizziness, tachycardia). Mental disorders are common, consisting of asthenia, slowing of memory and intellectual ability.[15]

The **differential diagnosis** is made with all other tumor arising in the sella turcica region including not only pituitary adenomas, but also hypothalamic and optic glioma, Rathke's cleft cyst, epidermoid tumor, thrombosis of the arachnoid cyst, third ventricle cyst, hystiocytosis.[16]

Neuroradiological Examination

On paraclinical examination, the radiography provides important information about the size of the sella turcica, and the presence of calcifications. The CT examination found the presence of calcifications in a proportion of 100% in the pediatric population while for adults

around 48%. Regarding the histopathological types, adantinomatous CP presents in 83.3% of calcification cases. The T1 bright signal due to an increased amount of protein, cholesterol or bleeding was observed in 73.3% of cases of Adantinomatus, and only 25% in the case of papillary CP.[17]

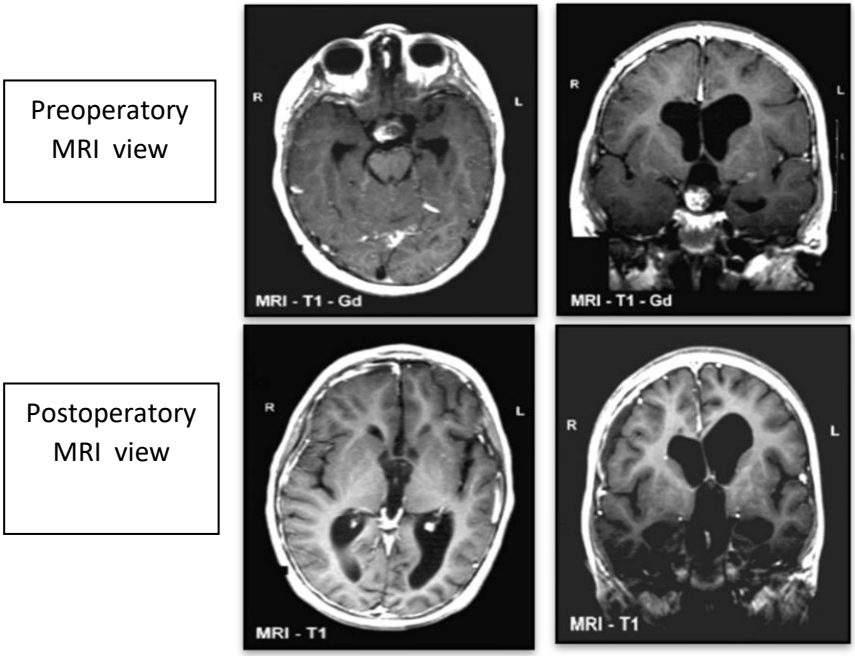

Figure 2. MRI presenting CP in male patient, no endocrine deficit, visual impairment. Treatment of choice total resection. Postoperative status has been improved.
(Personal collection of Prof.dr.A.V.Ciurea)

Usually as many tumors, CP seems to be more T1-weighted hyperintense and low in T2-weighted imaging. However, there may be situation when due to local haemorrhage when CP appears brighter on T2-weighted imaging. Size on the MRI varies most of the tumors being between 2 and 4 cm (58-76%), but there were also reported cases of giant

CP predominantly with cystic composition.[18] The most frequent location of CP is in the suprasellar region with a small portion entering the sella diaphragm. Exclusive intrasellar tumors are rare.[16]

Prognostic based on the MRI examination was also proposed by De Vile et al. in the population of pediatric patients where tumors at 3.5 cm height, hypothalamic injuries association, and intra-operative adherence of the tumor to the floor of 3rd ventricle leads to increased morbidity.[19]

In the context of the classification of craniopharyngiomas, M. Samii et al. introduced in 1997 the classification of CP according to optical chiasm.[20] Thus, he deduced that about a third of tumors are subchiasmatic, 20% are prechiasmatic, 10-15% are intrasellar. The personal classification of the author can be found in Ciurea et al. 2003 which states that CP is divided into 5 categories: intrasaddle, supersaddle and retrochiasmatic - the most common, retrochiasmatic supersaddle with anterior extension, retrochiasmatic supersaddle with posterior extension and retrochiasmatic supersaddle with extension in the ventricle 3.[21]

Other classification was reported by Puget et al. who have presented a pediatric CP classification according to the hypothalamic involvement. In his classification, the treatment should be chosen according to the involvement of the neurovascular structure. Type 0 (no involvement) and type 1 (slight elevation of the hypothalamus) should be recommended to the gross-total resection with preservation of the neuroendocrine functions. In case of type 2 tumors (hypothalamus is no longer visible on the MRI), gross-total resection is not recommended due to increased morbidity. Yet, the discussion in such a situation is raised whether or not the function of the hypothalamus could be restored. This question depends also on the preoperative hormonal status of the patient.[22]

Treatment

The treatment used depends on the location, the spread of the tumor, the symptoms and is variable. Gross-total tumor resection, partial resection with Gamma-Knife Surgery (GKS) or radiation therapy, cyst decompression, or adjuvant drug therapy for endocrine

dysfunction may be applied. In preparing for surgery, important neurovascular aspects of the region such as the hypothalamus, optic tract, pituitary tuberculae, internal carotid branches should be considered. Some particular situations that complicate tumor resection would be its adhesion to the antero-inferior wall of the hypothalamus, or the intraventricular extension of the tumor, in this case the infiltration of the walls being very common. In these situations, total resection is almost impossible, and the tumor is hardly separated from the nerve structures.[23,24]

The dissection of the prechiasmatic regions, the retrochiasmatic space and the opticarotid triangle should be extended as much as possible. Opening of the terminal lamina without injury to the vascular bundle is necessary when the tumor is located in the ventricle.

The dimension of sella opening has an important impact on the CP invasion in the infrasellar region. The greater the opening, the more invasive the tumor is in the inferios part of the sellar region. Some important barriers in preventing CP invasion of the neurovascular structures are the arachnoid of the pituitary stalk, the Lilequist membrane and the membrane covering the ICA. While the tumours arising below the sellar diaphagm involved more often the pituitary gland, tumours arising from the upper part of the pars tuberalis appears to be more involved in the invasion of the 3rd ventricle.

Obtaining total resection is the gold standard in the treatment of craniopharyngiomas. Total resection was associated with minimal recurrence (10.7%), and 81.8% of patients improved their vision without worsening neurological status.[25]

The most suitable intervention is the **extended endoscopic transsphenoidal** approach with several limitations such as the impossibility to resect to entire tumor, tumor invading neurovascular structures or multiple fossae, tumor adherent to the brain tissue postradiation. In the extended endoscopic approach, the dura is opened and the below the diaphragm sella but up to the pituitary gland. Once the endoscope is entered into the sphenoid sinus the tumor capsule is often observed in the upper part of the cavity. The vessels of the capsule should be cauterized before debulking the capsule. First the cystic part

is evacuated, second the solid part and then any adherent wall part to the neurovascular structures.

The pterional approach is the most often used because it consists of the shortest way to reach the CP. This approach can be associated with any tumor extension in the prechiasmatic or retrochiasmatic area. The dimension of the incision is adapted to the tumoral invasion, being more posterior when the tumor invades the posterior fossa. Great attention should be paid when approaching the posterior part of the ipsilateral optic nerve, the infundibular part and third ventricle using pterional approach. For the **subfrontal approach** a bicoronal incision is perfomed, followed by gently frontal lobe retraction.[26] Once the bilateral optic nerves are observed careful dissection should be followed. This approach offers great access to the tumor involving the optico-chiasmatic cisten and suprasellar region tumors.[27]

The midline approaches consist of interhemipsheric transcallosal approach used for intraventricular tumors. The transventricular approach or transcallosal approach are often used for the tumors located intraventricular. An intraventricular tumor is hard to be resected completed, therefore preoperative imaging should serve as a tool for understanding the level of invasion. In a study by Pascual et al. he demonstrated that in 83% of the cases the angle between the Mammillary Bodies and the floor of the fourth ventricle serve as a measure tool for third ventricular involvement of the tumor.[28] A curvilinear incision is made centered at the coronal suture. After careful retraction of the brain, the ventricle is penetrated. Before tumor debulking, the ventricle should be observed. Usually in case of chronic hydrocephalus the foramen Monroe is widely dilated. If the tumor extends also to the lateral ventricles, this detail would be visible at this moment. In the transcallosal approach the incision is similar, but more medial, which pose a greater risk of sagittal sinus injury. Once the corpus callosum is visualized it is recommended to perform a small incision in line with foramen Monroe. Complications of the procedure are epileptic attacks and memory deficits due to fornix injury.[29]

Yet, complications that appear after this aggressive first two approaches may be overcome by using a **frontobasal anterior approach**. This approach permits to resect tumors involving both

anterior intraventricular space and interpeduncular cistern. After a coronal incision and dura cut, the optic chiasm and anterior communicating artery at the genus of corpus callosum is exposed. Such an approach provides gross-total resection in 18 out of 20 cases without pituitary stalk injury. Complications of this procedure may arise from stretching of the frontal lobe. Some aspects used in the last approach consist in the drilling of the sphenoid bone making more access to the tumor in the prechiasmatic area or in the infrasellar region and detachment of the anterior communicating artery to increase the visual space in the lamina terminalis. The lateral approach consists of frontotemporal approach and subfrontal approach.[30]

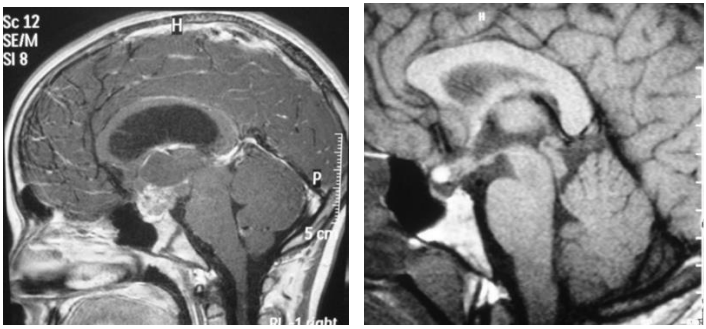

Figure 3. Total Removal of Craniopharyngioma, no recurrence, obesity, corticotherapy. Second picture – follow-up at 8 years.[10]
(Personal collection of Prof.dr.A.V.Ciurea)

The most **common complications** after surgery are neuroendocrine dysfunctions, visual disturbances, anosmia, hypothalamic dysfunction, 3rd nerve palsy, internal carotid artery branches injury, seizures, subdural effusion and hypopituitarism.

The most common neuroendocrine dysfunction is **diabetes insipidus (DI).** Thus, monitoring the fluid intake and sodium in serum postoperative is mandatory. The postoperative polyuria could be a sign of the onset of diabetes and the treatment should be administrated promptly (desmopressin). There may be situations when DI have been for a long period a symptom in the life of patient. In such situation, a more aggressive tumor resection may be recommended since the

restoration of the neuro-endocrinopathy may be impossible. The onset of DI has been manifested in 3 phase: endogenous secretion of vasopressin immediate postoperative with a peak at 24 hours, then an improper vasopressin secretion causing hyponatremia, and final the later stage of DI at 2 weeks postoperative.[31] Later the evolution of the dysfunction could be complicated with cerebral salt wasting, with thirst abnormalities (adipsia) leading in some situation to hypernatremia, developing tachycardia and sunken eyes.[32] Complications are often encountered in the transcranial group than in the transphenoidal group. The rate for Diabetes insipidus is twice more in the open surgery than in the endonasal approach, while hemorrhage complications are at the same rate between both procedures.[33] Diabetes Insipidus could be transient or permanent, and could be determined because of mechanical trauma during surgery or because of the ischemia postoperative.

Hypopituitarism is a frequent complication after the surgery of CP. Deficient of growth hormone (GH), thyroid hormone and adrenocorticotropic hormone has been reported. Patients with GH substitutive therapy have reported better Quality of Life (QoL) then patients without it. Despite GH deficiency, some patients still reported accelerated growth status. One possible explanation for this would be IL-1 secretion by the hypothalamus leading to hyperphagia and hyperinsulinism and accelerated growth.[34] GH therapy does not lead to an increase in the tumor, but contrary, it has been reported that patients who have been administered GH have reported lower rates recurrence. GH trigger the release of IGF-1, a protein which is implicated in carcinogenesis and metastasis. It is debatable at which extend GH substitution therapy may lead to cancer.[35]

Hypothalamus injury is linked to metabolic severe dysfunctions related to obesity. Over 50% of the patients start to develop obesity and have reported a lower QoL after surgery. Hyperphagia and lower energetic expenditure can contribute to obesity development. Sella massive tumors have associated with lower postoperative QoL due to associated comorbidities and higher BMI (body mass-index) at presentation. Hyperinsulinemia and leptin resistance are also linked to obesity onset.[36] There are several which contributes to the onset of

obesity namely: tumor location in hypothalamus or thalamus, concurrent hormonal deficiency. Thus patients reported GH deficiency or thyroid hormone deficiency were more predisposed to develop obesity. The imbalance between satiety and appetite or an autonomic dysfunction of the vegetative system may be among the causes. GLP-1 analogues are a solution for determining satiety in this kind of patients, leading to stimulation of insulin and glycogen secretion.[37] Extensive hypothalamic surgery have been associated with worse postoperative status than hypothalamus sparing surgery with adjuvant radiotherapy and there were no differences in the recurrence rate between aggressive surgery and sparing surgery.[38]

One of the main goals of the surgery is the improvement of the **visual disturbances**. Very often CP surrounds the optic chiasm, having a mass effect on the optic path. Visual disturbances are improved in 33.1% of the cases while 37.1% of the cases remains stable in transcranial approach, while in the endoscopic approach 56.2% of the patients have improved their visual disturbances and 10.7% remained stabled.[33] Fahlbusch et al. reported no visual disturbances after transsphenoidal approach while there were 14.3% worsening in the group of the transcranial approach.[39] Postoperative visual disturbances have several causes such as mechanical trauma of the visual tracks, ischemic lesions that appear perioperative, postoperative hematoma with mass effect. Thus, preserving the vasculature during surgery especially the direct branches from the carotid artery has an important on the follow-up evolution of the symptoms. In order to preserve the optic chiasm, CP should be targeted with precision. Tumors located in the pre-chiasm region should approached via endonasal or supraorbital, while tumors extending laterally via anterior supraorbital approach or via a lateral approach.

Other postoperative complications consist of the vascular lesions such as dilacerations of the carotid artery, aneurysm formation or vasospasm. Vasospasm have several causes such as the postoperative subarachnoid bleed, degradation bio-products of the blood. Mechanical trauma that triggers release of the blood chemical components may trigger late vasospasm.[40]

Other complications associated especially with the surgical approach were CSF leakage which is more often reported in the transsphenoidal surgery which are treated by introducing of nasoseptal flaps. Seizures is another complication encountered especially in case of transcranial surgery when the approach is closer to the nervous structures such as fornix or corpus callosum. Anti-epileptic treatment postoperative is administrated in such situations. Meningitis due to bacterial infection, nerve palsy and anosmia are other complications.

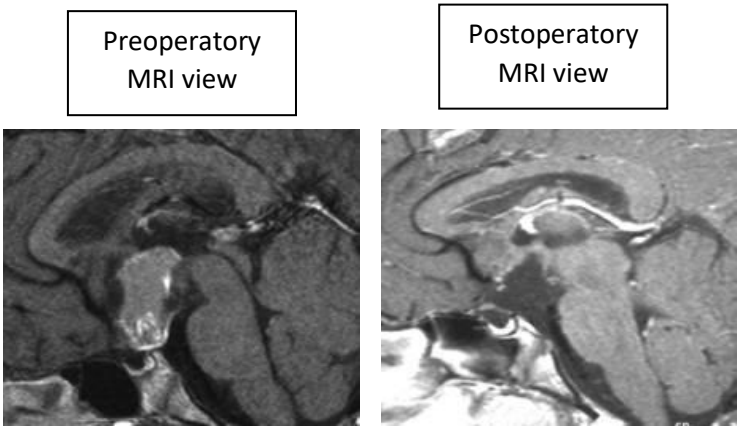

Figure 4. Case report: 10 years girl with endocrine dysfunction, raised intracranial pressure, visual impairment after total resection of CP via bilateral subfrontal approach. Second picture – 9 years follow-up, patient experienced improvement of quality of life.
(Personal collection of Prof.dr.A.V.Ciurea)

Even though complete resection is a gold standard in the CP since their benign nature, preoperative size, tumor invasion and neurovascular adherence could lead to the necessity of using partial surgery in order to preserve the functionality of the structures. Thus, whether partial surgery alone or **partial surgery** combined with **radiotherapy** are options to be discussed in the management of CP. Introduction of radiotherapy after partial resection is a debatable topic at this private time. Radiotherapy uses a focal beam of radiations

administred to an area calculated according to the MRI or CT called the gross-total volume. If to this volume, 3-5 mm margin is added then the overall volume will be called the planning target volume. This method has the disadavantage of no reliable protection of the surrounding normal tissue.[41] It has been found that early introduction, immediately after surgery when the tumor is still at a low level, has a much better beneficial effect on the patient medical's progress. Delayed introduction of radiation therapy leads to loss of visual sensitivity and early onset of diabetes insipidus.[42] Personally, the authors do not recommend using radiation therapy in children because of the increased toxic effects that therapy may have. Stripp et al. analyses the comparision between surgery alone and subtotal resection combined with RT. Even though overall survival rate was similar in both groups, he concluded that surgery alone express 42% local control to 84% local control in the combined group.[43]

Radiation of the cystic CP have been associated with the risk of enlargement of the cyst which could be transient or permanent and could affect or not the neurovascular structures. In case of a permanent cysts growth, urgent surgery should be promptly performed. Cysts enlargement was not associated with beam fraction, dose of the radiation or irradiation procedure.[18]

Among the complications of radiotherapy (RT) are visual loss and cognitive outcomes. Visual loss was well-documented in the literature and was associated with cyst regrowth. Decompressive craniotomy or cyst aspiration could reverse the effect if the procedure is applied in the right time. Endocrine dysfunctions were also related to radiotherapy. 70% of the children after radiotherapy needed GH supplements and 90% required thyroid replacement.[44] Radiation necrosis can be a complication of RT that could take place immediate after RT or on the long evolution. Necrosis of the cells in the pituitary and hypothalamic region could lead to hormone defficiency. RT was also associated with other malignancies.[45]

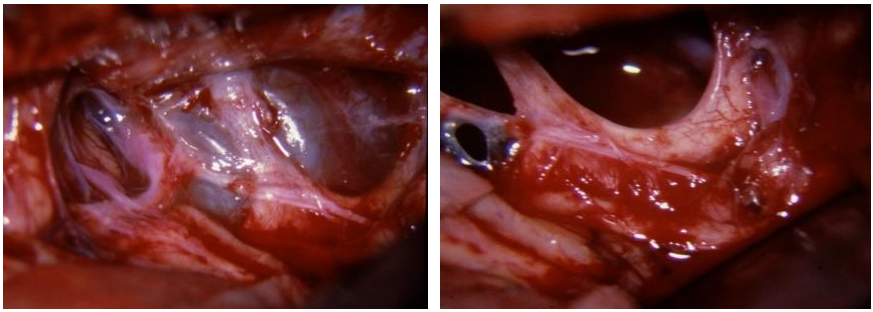

Figure 5. Intraoperative Microsurgical dissection – first picture: before tumor resection, before vascular dissection – second picture: optic chiasm is visible and tumor is resected.
(Personal collection of Prof.dr.A.V.Ciurea)

Gamma-Knife Surgery (GKS) treatment brings promising results with a survival rate of 96% in the first 5 years and 86% in the first 10 years. The analysis score of the skills to carry out the activity was 76% at 5 and 10 years.[46] In another study by Lee et al. local tumor control was influenced by the type of the tumor being (73.9% for cystic, 66.3% for mixed group). The overall survival rate was 91.5% and 83.9% at 5 and 10 years. 8% of the patients felt worsening pituitary status. [47] GKS implies that the tumor should be solid, well-circumscribed on the MRI, its dimension < 3 cm , and with safety margin of 3 mm from the neurovascular structures around the tumor.

The advantage of GKS is that it implies excellent coverage of the tumor, and no dose is administred to non-target tissue. Disavantage consists of the limited clinical settings, and the questions is raised the tumor control is low in quality comparative to the fractioned therapy.[41]

Large cysts are responsible for producing mass effects, compressing the hypothalamus, optical chiasm and pituitary stalk. A subgaleal Ommaya Reservoir is the solution in case of large cysts situated in the suprasellar region. The rapid drainage ameliorates the symptoms and may allow for a surgical intervention in removing the cyst. After cyst shrinkage, a catheter is placed under stereotactic guidance or under endoscopic visualization that connects the cyst with the reservoir.[48]

Ommaya Reservoir have accomplished tumor control around 72% of the cases, that were similar with that accomplished with endoscopic treatment 75%. GKS was lower, around 66%.[48] Moussa et al. reported 73% tumor control just using stereotatic Ommaya reservoir without any further treatment. In his study, he advocates for the use of Ommaya reservoir as the primary treatment in case of cystic tumors.[49]

In conclusion, craniopharyngiomas are rare benign tumors, but very common in the pediatric population with a high survival rate. Their complexity resides in the strategic position of the tumor around the principal neurovascular elements in the brain which made for a long time to be considered a purely surgical disease. Currently, craniopharyngiomas approach involves a multimodal perspective including neurosurgeons, neuroradiologists, endocrinologists, neurologists and ophtalmologists. Surgery of craniopharyngiomas has been evolved so much in the past years and the survival rate have increased considerable. A strategic surgical planning is important to make the difference between the quality of Life of the patients. Primary tumor size, admission symptoms, level of resection, multimodality approach, irreversible dysfunctions belongs to a wide plethora of characteristics that defines this complex pathology.

Abbreviations:
CP – craniopharyngiomas
GKS – Gamma-Knife Surgery
CPAd - Adamantinomatous craniopharyngiomas
CPPap – Papillary craniopharyngiomas
GH – growth hormone
QoL – Quality of Life
RT – Radiotherapy
CSF – cerebrospinal fluid
ICP – intracranial pressure
BMI - body mass-index

Disclaimer: No conflict of interest. No financial support. Literature Review

References:

1. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM. The descriptive epidemiology of craniopharyngioma. J Neurosurg. 1998; 89(4):547-51.
2. Matson DD, Crigler JF Jr. Management of craniopharyngioma in childhood. J Neurosurg. 1969; 30(4):377-90.
3. Zacharia BE, Bruce SS, Goldstein H, Malone HR, Neugut AI, Bruce JN. Incidence, treatment and survival of patients with craniopharyngioma in the surveillance, epidemiology and end results program. Neuro Oncol. 2012; 14(8):1070-1078.
4. Müller HL, Merchant TE, Warmuth-Metz M, Martinez-Barbera JP, Puget S. Craniopharyngioma. Nat Rev Dis Primers. 2019; 5(1):75.
5. Hölsken A, Kreutzer J, Hofmann BM, Hans V, Oppel F, Buchfelder M, Fahlbusch R, Blümcke I, Buslei R. Target gene activation of the Wnt signaling pathway in nuclear beta-catenin accumulating cells of adamantinomatous craniopharyngiomas. Brain Pathol. 2009 Jul;19(3):357-64.
6. Larkin, S.J., Preda, V., Karavitaki, N., Grossman, A., Ansorge, O., 2014. BRAF V600E mutations are characteristic for papillary craniopharyngioma and may coexist with CTNNB1-mutated adamantinomatous craniopharyngioma. Acta. Neuropathol.
7. Yachnis T. Craniopharyngioma: Embryology, Pathology, and Molecular Aspects. In: Kenning TJ, Evans JJ, editors. *Craniopharyngiomas: A Comprehensive Guide to Diagnosis, Treatment and Outcome.* Elsevier Science; 2015. pp. 95–105.
8. Miller DC. Pathology of craniopharyngiomas: clinical import of pathological findings. Pediatr Neurosurg. 1994;21 Suppl 1:11-7.
9. Lubuulwa J, Lei T. Pathological and Topographical Classification of Craniopharyngiomas: A Literature Review. J Neurol Surg Rep. 2016; 77(3):e121-e127.
10. Ciurea AV, Saceleanu V, Mohan A, Moreanu MS, Toader C. Craniopharyngiomas in children - experience of consecutive 152 operated cases. Acta Endocrinol (Buchar). 2020;16(1):103-109.
11. Ortiz Torres M, Shafiq I, Mesfin FB. Craniopharyngioma. [Updated 2020 May 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan.
12. Müller HL, Gebhardt U, Etavard-Gorris N, Korenke E, Warmuth-Metz M, Kolb R, Sörensen N, Calaminus G. Prognosis and sequela in patients with childhood craniopharyngioma -- results of HIT-

ENDO and update on KRANIOPHARYNGEOM 2000. *Klin Padiatr.* 2004;**216**(6):343–8.
13. Caldarelli M, Massimi L, Tamburrini G, Cappa M, Di Rocco C. Long-term results of the surgical treatment of craniopharyngioma: The experience at the Policlinico Gemelli, Catholic University, Rome. Child's Nerv Syst. 2005;21(8–9):747–57
14. Nuijts MA, Veldhuis N, Stegeman I, et al. Visual functions in children with craniopharyngioma at diagnosis: A systematic review. PLoS One. 2020;15(10):e0240016.
15. Mohan D, Ciurea AV, Mohan AG. Craniofaringioamele. In: Mohan D, Ciurea AV, Mohan AG, editors. *Curs de Neurochirurgie.* Editura Universitatii din Oradea; 2014. pp. 187-188.
16. Müller HL. Craniopharyngioma. Endocr Rev. 2014;35(3):513-43.
17. Lee lH, Zan E, Bell WR, Burger PC, Sung H, Yousem DM. Craniopharyngiomas: Radiological Differentiation of Two Types. J Korean Neurosurg Soc. 2016; 59(5):466-470.
18. Karavitaki N, Wass JA. Craniopharyngiomas. Endocrinol Metab Clin North Am. 2008;37(1):173-93, ix-x.
19. De Vile CJ, Grant DB, Kendall BE, Neville BG, Stanhope R, Watkins KE, Hayward RD. Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? J Neurosurg. 1996;85(1):73-81.
20. Samii M., Tatagiba M. Surgical Management of Craniopharyngiomas: A Review. *Neurologia Medico-Chirurgica.* 1997;37(2):141–149.
21. Ciurea AV, Mircea D, Coman Teodora, Vionescu D, Tascu A, Lisievici M. Our policy in craniopharyngiomas – comparative studies in children and adults – a personal craniopharyngiomas grading scale, In: Brain Tumor Surgery; Management Strategies and Navigator / Neuroendoscope Osaka, Medica Co. *Noboru Sakai.* 2003; 1:145–157.
22. Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N. Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. *J Neurosurg Pediatr.* 2007;106:3–12.
23. Yasargil MG, Curcic M, Kis M et al (1990) Total removal of craniopharyngiomas. Approaches and long-term results in 144 patients. J Neurosurg 73:3–11

24. Choux M, Lena G (1998) Craniopharyngioma. In: Apuzzo MLJ (ed) Surgery of the third ventricle, vol 2. Williams and Wilkins, Baltimore, pp 1143–1181
25. Zieliński G, Sajjad EA, Robak Ł, Koziarski A. Subtemporal Approach for Gross Total Resection of Retrochiasmatic Craniopharyngiomas: Our Experience on 30 Cases. World Neurosurg. 2018;109:e265-e273.
26. Aryan, Henry & Ozgur, Burak & Jandial, Rahul & Levy, Michael. (2005). Subfrontal transbasal approach and technique for resection of craniopharyngioma. Neurosurgical focus. 18. E10.
27. Lemole GM Jr, Henn JS et al (2003) Modifications to the orbitozygomatic approach: technical note. J Neurosurg 99:924–930
28. Pascual JM, Prieto R, Carrasco R, Barrios L. Displacement of mammillary bodies by craniopharyngiomas involving the third ventricle: surgical-MRI correlation and use in topographical diagnosis. J Neurosurg. 2013; 119(2):381-405.
29. Sivakumar W, Krisht KM, Couldwell WT. Surgical Approaches: Transcortical-Transventricular Removal of Craniopharyngioma. In: Kenning TJ, Evans JJ, editors, *Craniopharyngiomas.* Academic Press; 2015: pp. 219-230.
30. Xing H, Xing H, Hui P, Yang B. Removal of craniopharyngioma via fronto-basal interhemispheric approach. Oncol Lett. 2016;12(1):147-149.
31. Ghirardello S, Hopper N, Albanese A, Maghnie M. Diabetes insipidus in craniopharyngioma: postoperative management of water and electrolyte disorders. J Pediatr Endocrinol Metab. 2006;19 Suppl 1:413-21.
32. Raghunathan V, Dhaliwal MS, Gupta A, Jevalikar G. From cerebral salt wasting to diabetes insipidus with adipsia: case report of a child with craniopharyngioma. J Pediatr Endocrinol Metab. 2015; 28(3-4):323-6.
33. Komotar RJ, Starke RM, Raper DM, Anand VK, Schwartz TH. Endoscopic endonasal compared with microscopic transsphenoidal and open transcranial resection of craniopharyngiomas. World Neurosurg. 2012; 77(2):329-41.
34. Jensterle M, Jazbinsek S, Bosnjak R, et al. Advances in the management of craniopharyngioma in children and adults. Radiol Oncol. 2019;53(4):388-396.
35. Alotaibi NM, Noormohamed N, Cote DJ, et al. Physiologic Growth Hormone-Replacement Therapy and Craniopharyngioma

Recurrence in Pediatric Patients: A Meta-Analysis. World Neurosurg. 2018; 109:487-496.e1.
36. Roth CL. Hypothalamic Obesity in Craniopharyngioma Patients: Disturbed Energy Homeostasis Related to Extent of Hypothalamic Damage and Its Implication for Obesity Intervention. J Clin Med. 2015;4(9):1774-1797.
37. Castro-Dufourny I, Carrasco R, Pascual JM. Hypothalamic obesity after craniopharyngioma surgery: Treatment with a long acting glucagon like peptide 1 derivated. Endocrinol Diabetes Nutr. 2017; 64(3):182-184.
38. Elowe-Gruau E, Beltrand J, Brauner R, Pinto G, Samara-Boustani D, Thalassinos C, Busiah K, Laborde K, Boddaert N, Zerah M, Alapetite C, Grill J, Touraine P, Sainte-Rose C, Polak M, Puget S. Childhood craniopharyngioma: hypothalamus-sparing surgery decreases the risk of obesity. J Clin Endocrinol Metab. 2013; 98(6):2376-82.
39. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M. Surgical treatment of craniopharyngiomas: experience with 168 patients. J Neurosurg. 1999;90(2):237-50.
40. Salunke P, Sodhi HB, Aggarwal A, Ahuja CK. Delayed cerebral vasospasm following surgery for craniopharyngioma. J Neurosci Rural Pract. 2013; 4(1):107-9.
41. Kortmann RD. Different approaches in radiation therapy of craniopharyngioma. Front Endocrinol (Lausanne). 2011; 2:100.
42. Varlotto J, DiMaio C, Grassberger C, Tangel M, Mackley H, Pavelic M, Specht C, Sogge S, Nguyen D, Glantz M, Saw C, Upadhyay U, Moser R, Yunus S, Rava P, Fitzgerald T, Glanzman J, Sheehan J. Multi-modality management of craniopharyngioma: a review of various treatments and their outcomes. Neurooncol Pract. 2016; 3(3):173-187.
43. Stripp DC, Maity A, Janss AJ, Belasco JB, Tochner ZA, Goldwein JW, Moshang T, Rorke LB, Phillips PC, Sutton LN, Shu HK. Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. Int J Radiat Oncol Biol Phys. 2004 ;58(3):714-20.
44. Kiehna EN, Merchant TE. Radiation therapy for pediatric craniopharyngioma. Neurosurg Focus. 2010; 28(4):E10.

45. Kalapurakal JA. Radiation therapy in the management of pediatric craniopharyngiomas--a review. Childs Nerv Syst. 2005; 21(8-9):808-16.
46. Kobayashi T, Tsugawa T, Hatano M, Hashizume C, Mori Y, Shibamoto Y. Gamma knife radiosurgery of craniopharyngioma: results of 30 cases treated at Nagoya Radiosurgery Center. Nagoya J Med Sci. 2015; 77(3):447-454.
47. Lee CC, Yang HC, Chen CJ, Hung YC, Wu HM, Shiau CY, Guo WY, Pan DH, Chung WY, Liu KD. Gamma Knife surgery for craniopharyngioma: report on a 20-year experience. J Neurosurg. 2014 Dec;121 Suppl:167-78.
48. Frio F, Solari D, Cavallo LM, Cappabianca P, Raverot G, Jouanneau E. Ommaya Reservoir System for the Treatment of Cystic Craniopharyngiomas: Surgical Results in a Series of 11 Adult Patients and Review of the Literature. World Neurosurg. 2019 Dec;132:e869-e877.
49. Moussa AH, Kerasha AA, Mahmoud ME. Surprising outcome of ommaya reservoir in treating cystic craniopharyngioma: a retrospective study. Br J Neurosurg. 2013;27(3):370-3.

PITUITARY ADENOMA

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People fall into two categories: some who seek and cannot find, others who find and are not satisfied.
Mihai Eminescu, Romanian poet (1850-1889)

Contents

1. Introduction

The expansive processes of the Sellar region include: tumors of mesenchymal origin, neural or epithelial, metastasis, as well as cystic or inflammatory lesions. Among the epithelial tumors, most are **pituitary adenomas,** benign tumors that develop from the cells of the adenohypophysis , constituting approx. 10-15% of all intracranial neoplasms, being much more common in adults . Symptomatic pituitary adenoma are present at **0.8-1% of the population**. Given the existence of asymptomatic pituitary adenoma, accidentally discovered at autopsy and having small dimensions (of the order of millimeters), found in over 25% of non-selected autopsied cases, and the incidence of adenomas is in fact much bigger. By immunohistochemical methods, these asymptomatic tumors have been shown to be non-secreting microadenomas or microprolactinomas.

Another category of pituitary tumors, much more aggressive, but also extremely rare, is pituitary carcinomas which were reported only in 0.2% of surgical cases. From a morphological point of view, adenomas and carcinomas do not differ from each other, the latter being distinguished by the presence of cerebrospinal or systemic metastases.(1)

According to clinical criteria, pituitary tumors can be grouped into **inactive endocrine (non-secreting)** and **active endocrine (secreting).** Of the total pituitary adenomas, the non-secretory ones represent 25-30%, prolactinomas and adenomas secreting somatotropic hormone (growth hormone-GH), each approx. 30%, adenocorticotropic hormone-secreting adenomas (adenocorticotropic hormone-ACTH) 5-10%, thyroid hormone-secreting adenoma (TSH) less than 1%, follicle-stimulating hormone-secreting adenoma (FSH)) or luteinizing hormone-secreting adenoma (LH) being rare. Also, approx. 10% of adenomas are mixed tumors, 75% of which are macroadenomas. (2)

The purpose of approaching this issue is to systematize the main information related to pituitary tumors, while updating them with recent data from the literature, the emphasis being on neurosurgical aspects.

2. Historical data

Known since antiquity, the pituitary gland, also called the "pituitary organ", began to be studied in detail, morphologically and physiologically, only in the nineteenth century, by describing the cellular structure of the anterior pituitary and pituitary adenomas, first mentioned by Fritzche and Klebs (1884). Subsequently, the histological typology was associated with different clinical pictures. Carl Benda (1900) was the first to identify the origin of these tumors as being in the cells of the adenohypophysis. (2)

Over time, the diagnosis has been refined with neuroimaging technology and surgical technique with the improvement of intraoperative lighting, by introducing the operating microscope. The transphenoidal approach was introduced by Harvey Cushing (1910).

Recently, pituitary tumor surgery was the first neurosurgical branch to use intraoperative neuronavigation, associated with intraoperative MRI control. (3) The chronology of the most important moments in the modern history of the diagnosis and treatment of pituitary tumors is presented in table 1. (3)

The evolution of drug therapy of pituitary tumors is marked by the following moments: the introduction of adrenolytic agents (late ' 50s) in the treatment of Cushing's disease, a b romocriptine for the treatment of prolactinomas (1970) and the discovery of suppression of GH secretion by somatostatin (1973), followed by research on obtaining increasingly effective forms of GH antagonists and agonists. (4)

Table 1. Highlights from the modern history of the diagnosis and treatment of pituitary tumors.

Highlights	Contribution to the diagnosis and treatment of hypophysical tumors	Year
Flesch, Lothriger, Dostoiewski	Use of hemotoxylin-eosin staining to describe adenohypophyseal cell types	1844 -1886

Highlights	Contribution to the diagnosis and treatment of hypophysical tumors	Year
Fritzche, Klebs	Acromegaly associsted with adenohypophysis tumour and first use of the term pituitary adenoma	1884
Sir V. Horsley	Subtemporal transcranial approach	1889
H. Oppenheim	Radiological description of sella turcica dilation in pituitary tumors	1899
C. Benda	Opening of the modern era in the histopathology of pituitary tumors: demonstration that pituitary tumors are adenomas developed from adenohypophyseal cells	1900
F. Krause	Subfrontal transcranial approach	1904
H. Schloffer	Transsphenoidal approach by rhinotomy (local anesthesia)	1907
N. Paulescu	Experimental studies on the clinical effect of partial and complete ablation of the pituitary gland	1907
A. Gramegna	Introduction of conventional external radiotherapy in the treatment of pituitary tumors	1909
H. Cushing	Description of the clinical conditions of hypo- and hyperpituitarism Cushing's approach: transseptal transsphenoidal approach (general anesthesia), headlamp illumination Subfrontal and subtemporal transcranial approach experimental studies on the effect of using pituitary extracts in pituitary animals Description of Cushing's disease	1909 1910 1912
O. Hirsch	Transseptal endonasal transfenoidal approach (local anesthesia)	1910

Highlights	Contribution to the diagnosis and treatment of hypophysical tumors	Year
	Description of the clinical picture of non-secreting pituitary tumors associated with visual disturbances	1911
W. Dandy	Use of pneumonencephalography as a diagnostic method	1919
N. Dott	Transfers the Cushing approach to Europe	
AP Forbes, E. Allbright	description of amenorrhea-galactorrhea syndrome	1954
G. Guiot	Transseptal sublabial transphenoidal approach intraoperative fluoroscopic control intraoperative optical magnification (magnifying glass) endoscopically assisted transsphenoidal approach	1956 1963
J. Hardy	Transseptal sublabial transphenoidal approach use of preoperative angiography and pneumoencephalography introduction of the operating microscope modern principles of selective transsphenoidal adenomectomy	1965 1967 1968
L. Leksell	Introduction of radiosurgery in the treatment of pituitary tumors	1968
P. Brazeau	Application of somatostatin in the treatment of GH-secreting tumors	1973
MO Thorner	Application of bromocriptine in the treatment of prolactinomas	1974
K. Kovacs, E. Horvath	Ultrastructural classification of pituitary tumors (electron microscopy) Immunohistochemical diagnosis	1976 1991

Highlights	Contribution to the diagnosis and treatment of hypophysical tumors	Year
RCL Guillemin, A. Schally	Discovery of neuropeptide hormones	1970-1980
R. Jankowski	Endoscopic approach to pituitary tumors	1992
AJ van der Lely	Application of pegvisomant in GH-secreting tumors	2001
R. Fahlbusch	Sublabial-endonasal transsphenoidal approach, introduction of intraoperative MRI control of tumor resection coupling neuronavigation with intraoperative MRI control of tumor resection	1999-2004

3. Etiology

The pathogenesis of pituitary tumors is not yet fully elucidated, and it is recognized that **tumorigenesis** can be induced by thyroidectomy and estrogen administration. Experimental animal studies have shown that hypothalamic factors cannot be excluded from the determinism of these tumors.

Recent research on the **behavior of genetic material** admits that genetic predisposition is involved only in the syndrome of multiple endocrine neoplasms type 1 (MEN1) (about 3% of pituitary tumors) and in GH-secreting familial adenomas. (4)(5)

The rest of the adenohypophyseal tumors are generated by **acquired genetic abnormalities**, initiated at the level of growth factor receptors, which lead to the modification of cytoplasmic cell signaling pathways and, finally, to pathogenic nuclear changes. Thus, alteration of individual genetic material is considered the predominant factor. It has been shown that there is an autonomy of pituitary cells, the mills appearing through a defect in the regulation of cytoplasmic activity, with a negative, secondary effect on the chromosomal material, which leads to an excessive monoclonal proliferation.

Molecular biology and immunohistochemistry studies have shown that, in addition to many other factors (angiogenesis, apoptosis, growth

factors, suppressor genes, oncogenes, and hormone receptors), the tumorigenic mechanism is also based on erroneous expression of transcription factors and co-factors of the nucleotide sequence in the structure of proteins (among them, Pit-1, Prop-1). Also, the proliferative mechanism may be supported by disruption of cell cycle regulator expression, including inhibitors such as p16, p18, p27, and stimulators such as p53.

In addition to genetic factors, tumorigenesis can also be influenced by **epigenetic factors**, acting intracellularly at the level of molecular structures other than nucleic acids (histone changes, posttranscription, regulation of hormone expression inside the tumor).

Pituitary tumors are more aggressive the more complex of the disturbances in the proliferative cells is.

4. Histopathology and immunohistochemistry

Classically, pituitary tumors were classified, depending on the color of hematoxylin-eosin staining in: chromophobe (SMT), acidophilic (GH-containing cells) and basophils (cells containing ACTH). The introduction of electron microscopy and the immunohistochemistry has allowed ordering them to clinicopathological entities.

WHO classification (2004) is based on their histological, histochemical, immunohistochemical and electron microscope character, which is combined with clinical and imaging details (6).

5. Clinical aspects

The clinical picture of pituitary tumors contains two broad categories of manifestations with slow progressive evolution, expressing, on the one hand, the effect of tumor compression on neighboring brain and vascular-nervous structures, and, on the other hand, the secretory or non-secretory character of the tumor formation. In rare cases (3% of reported surgical cases), tumors can be revealed by acute onset of pituitary apoplexy.

Tumor compression is specific to large tumors, being found in both secretory and non-secretory tumors , manifesting clinically through an endocrine and neurological, ophthalmic syndrome .

Ophthalmic syndrome is characterized by:

- visual disturbances such as unilateral or bilateral decrease in visual acuity, sometimes up to blindness;
- changes in the visual field (initially quadrantopsia or visual field defect limited to certain colors, then bitemporal hemianopsia typical of pituitary tumors);
- changes of the fundus of the eye, of the type of papillary pallor (initially temporal, with subsequent extension) and of the late optical atrophy; papillary edema occurs in the presence of intracranial hypertension;
- exophthalmos is unilateral or paresis of oculomotor nerves, which indicates damage to intracavernous structures.

The neurological syndrome is characterized as follows:

- headache, initially intermittent, caused by dural distension; subsequently, continue with intracranial pressure (and vomiting associated with papillary stasis), caused either by the volume of the largest tumor or secondary hydrocephalus:
- irritant or lesional pyramidal syndrome;
- psychiatric disorders;
- epileptic seizures;
- disorders of temperature regulation, sleep behavior of food (adiposity-genital syndrome) caused by compression of the hypothalamus;
- diabetes insipidus or hyperprolactinemia, caused by prolonged compression of the pituitary stem.

In the case of active endocrine pituitary tumors, endocrine syndrome appears with clinical manifestations specific to each hormone secreted in excess. (9)

a) Prolactinomas secrete prolactin inducing to the women the syndrome Forbes-Allbright characterized by disorders of the menstrual cycle (from hypomenorea to amenorrhoea) and galactorrhea present most often in men, the clinical picture is less obvious, with a decrease in potency and libido, as well as oligospermia, serum values of prolactin are correlated positively with the size of the tumor.

b) Somatotropinomas (GH-secreting adenomas) in excess, produce gigantism in children (the tumor forms before the growth of growth cartilage) and acromegaly in adults, clinically characterized by:

- dysmorphic facies (mandibular prognathism, macroglossia), enlargement of the extremities, kyphosis, thickening of the skin ;
- rheumatological complications (peripheral and spinal arthropathy);
- peripheral neuropathy, radicular syndromes, carpal tunnel syndrome, caused by compression of the nerve through the narrow area openings;
- cardiovascular manifestations (hypertension, registered in 35% of cases; acromegaly, cardiomyopathy, valvulopathies);
- visceral hypertrophy, especially affecting the liver, heart and spleen;
- metabolic complications (insulin- resistant diabetes mellitus);
- respiratory complications (sleep apnea, daytime sleepiness);
- increased tendency to esophageal cancers, the stomach, the colon or thyroid; increased frequency of melanogaster of the m s and lymph the m s.

c) Cushing's disease, caused by hypersecretory adenomas of ACTH (corticotropinomas), is clinically characterized by:

- facies in the “full moon”;
- obesity with axo-rhizomelic stature, with significant decrease in muscle mass ;
- stretch marks, hirsutism, hyperpigmentation, bruising, skin fragility ;
- psychological disorders (psychosis cortisone);
- high blood pressure resistant to antihypertensive medication;
- menstrual disorders, impotence, oligospermia.

d) Nelson Tumor, sellar formation, that can be complicated after resection with the adrenal insufficiency, manifested by clinical signs of pituitary insufficiency associated with increased pigmentation.

Pituitary apoplexy is a rare clinical syndrome that can be life-threatening. Its incidence is higher in the fifth decade of age, respectively in men compared to women, being reported especially in patients with non-secreting tumors (about 58% of cases) and

prolactinomas (about 18% of cases). The cause of its occurrence is hemorrhage and / or necrosis of the tumor tissue or, less frequently, of the pituitary gland, which produces a sudden increase in volume of the intrasellar content, followed by compression and ischemia of the adenohypophysis whose hormonal secretion, especially on the corticotropic axis, becomes acute insufficiency.

The precipitating factors of the apoplexy are: major surgeries (cardiac surgery, in particular), anticoagulant treatments, contraceptives, hypertension, discontinuation of octreotide or bromocriptine, administration of metirapone.

Its clinical signs consist of:

- brutal, violent headache;
- nausea, vomiting;
- photophobia;
- fever;
- alteration of consciousness;
- sudden deterioration of vision (decreased visual acuity and narrowing of the visual field) ;
- signs of oculomotor nerve damage (diplopia, eyelid ptosis).

6. Preoperative investigations

a. Biochemical diagnosis (hormonal dosages)

Either for the **diagnosis of pituitary tumors**, and to monitor post-operative pituitary function accurate assessment of the hormonal dosage is essential. For this, it is necessary to use a mandatory battery of tests to determine the serum concentration of prolactin, cortisol, free thyroxine (free T4-fT4), TSH, estradiol / testosterone, LH, FSH, somatomedin C (insulin-like growth factor 1- IGF-1) as well as electrolytes.

Because **prolactinomas** can benefit from drug treatment, the dosage of prolactin is paramount for their differential diagnosis. Normal serum values are 0-15 ng / mL in men and 0-15 ng / mL in women, respectively. Moderate growth with values between 25 and 80 ng / mL, may appear in any type of sellar tumor, that compressed the pituitary. With some uncertainty, values between

81 - 200 ng / mL suggest the existence of a prolactinoma. At values greater than 200 ng / mL, the diagnosis becomes certain.

For it will take pituitary-adrenal which has an important role in the diagnosis of pituitary insufficiency as well as in Cushing's disease, ACTH and cortisol hormone determination is essential, the latter having greater stability in the circadian cycle. In both men and women, normal serum cortisol values during the day are 138-690 nmol/L (5-25 ng/mL), and at night 0-276 nmol / L (0-10 ng/mL).

The normal range of ACTH serum lie within 4-22 pmol/L. Cushing's disease is characterized by a moderate increase in ACTH, and on the high-dose dexamethasone suppression test (8mg), plasma cortisol decreases by 50% of baseline. The stimulation test with corticoliberin (corticotropin releasing hormone - CRH), patients with Cushing's disease have a normal response or even exaggerated, while the patients with ectopic ACTH tumors secretion or those with tumors of the adrenal does not determine increase in cortisol or ACTH.

Growth hormone (GH) is secreted periodically, has a short half-life, being undetectable for most of the day. Normal serum GH values, determined under strictly basal conditions, are less than 8-10 μg / L (SI) or 8-10 ng / mL (conventional units).

A TSH level basal the upper limit of normal (normal values: 0.5 to 4, 5m U / L) in the presence of high levels of T3 (normal free T3 plasma: 3-9 pmol / L) and T4 (normal plasma free T4 values : 8-26 pmol / L) defines an inadequate secretion of TSH, characteristic for TSH-secreting pituitary adenomas.

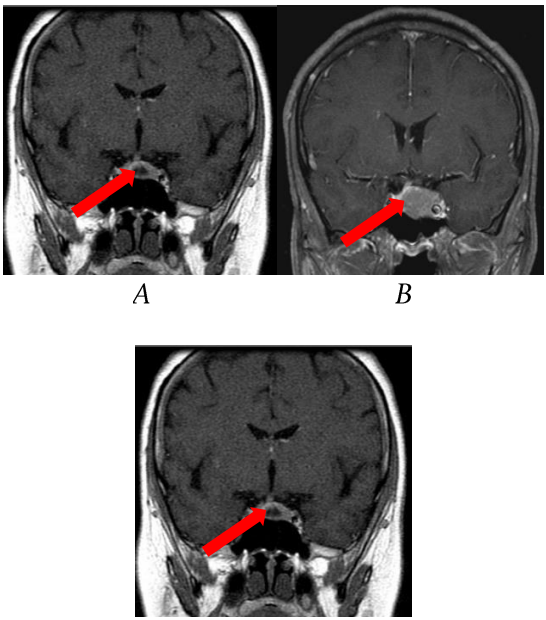
b. Imaging diagnosis of pituitary tumors

The small size of the pituitary gland, its proximity to important vascular-nervous structures, as well as the individual anatomical variability of the sellar region require that imaging diagnosis should use high-resolution and contrast equipment. Currently, **plain radiographs of the skull and sella turcica** is designed only to measure the degree of pneumatisation of sphenoid sinus, information provided on paranasal sinus pathology being vague compared to those purchased in high resolution technology. The changes to be noticed by simple radiography are the ballooning of the sella turcica, its double contour

(asymmetrical growth of the pituitary tumor), the thinning or destruction of the saddle dorsum.

The investigation of choice in cell pathology, including pituitary, is **brain magnetic resonance imaging (MRI)** (**Figure 1**). **Computed tomography (CT) of the brain** completes the diagnosis obtained by MRI, with information about the appearance of bone structures (anatomy of the sphenoid sinus, invasive tumors of the anterior stage of the skull base), calcifications and possibly bleeding (especially as an emergency investigation).

In terms of their size, pituitary adenomas are classified into **microadenomas** (tumors less than 1 cm in diameter), **macroadenomas** (tumors 1-4 cm in diameter) and giant adenomas (more than 4 cm in diameter) (figure 2).



A *B*

C

Figure 1. Characteristic aspect of a pituitary adenoma: A.Non-secreting. B. GH secreting C. ACTH secreting
(Personal collection of Dr. V. Gh. Ciubotaru)

Giant macroadenomas and adenomas usually enlarge the Turkish saddle, extending beyond its boundaries by infiltrating and / or eroding bone structures (sphenoid sinus, clivus, Turkish saddle floor), invading the cavernous sinus with embedding, not compression of the carotid artery. and by the superior extension to the optic chiasm, hypothalamus, and ventricle III which are compressed and possibly occupied. Also in this category is the possible presence of bleeding proliferative formations, intratumoral necrosis or cysts (Figure 2).

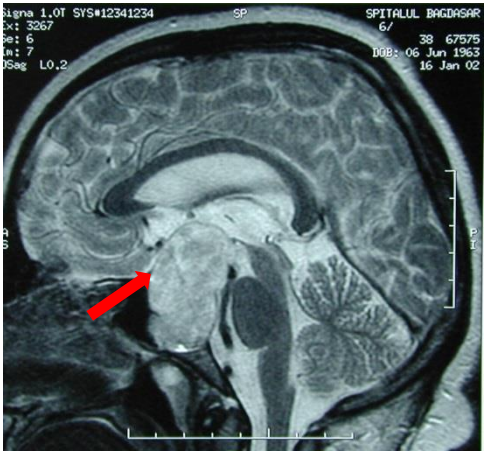


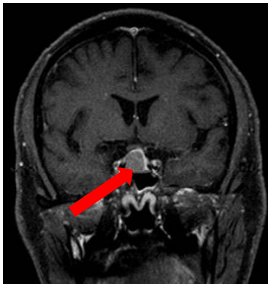
Figure 2. MRI: Giant pituitary adenoma
(Personal collection of Dr. V. Gh. Ciubotaru)

MRI examination also looks at the relationship between the pituitary tumor and the following vascular - nervous structures: optic chiasm, carotid arteries (intracavernous and supraclinoid portion), pituitary stem, suprachiasmatic cistern, ventricle III, cavernous sinuses.

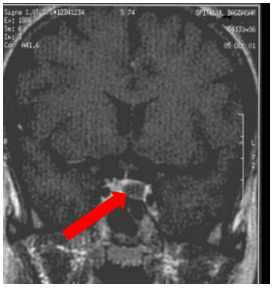
The invasiveness of pituitary tumors in the cavernous sinus structures is expressed by the Knosp scale, which defines the ratio between the extension / lateral invasion of the tumor in the cavernous sinus and the intercarotid line drawn through the center of the two sections of the intracavernous carotid artery (Table 3). Pituitary tumor invasiveness, according to the KNOSP scale positively correlated with their aggressiveness suggested by immunohistochemistry (Figure 3).

Table 3. Knosp scale - imaging classification of the invasion of pituitary tumors in the cavernous sinus. (10)

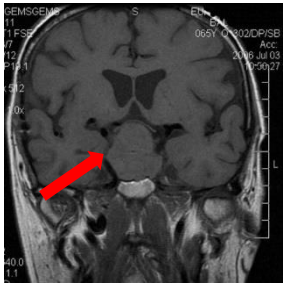
Degree of invasion	MRI visualization (coronary sections)
0	the tumor does not extend laterally tangent to the medial face of the intracavernous carotid artery
1	the tumor invades the cavernous sinus, but does not cross the intercarotid line
2	the tumor invades the cavernous sinus, but does not extend beyond the tangent to the lateral face of the intracavernous carotid artery
3	the tumor invades the cavernous sinus, exceeds the tangent to the lateral face of the intracavernous carotid artery, but does not completely encompass the intracavernous carotid artery
4	the tumor completely encompasses the intracavernous carotid artery



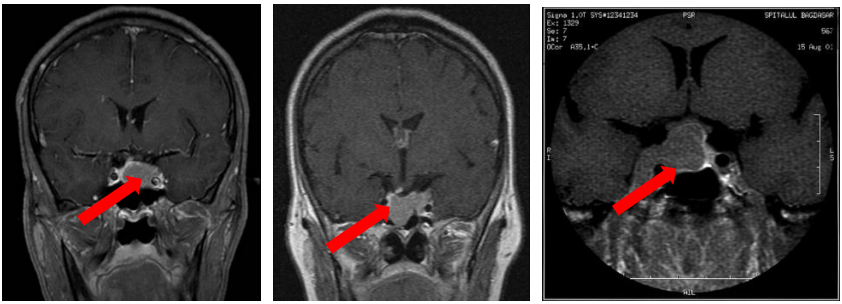
KNOSP 1/0



KNOSP 0/0



KNOSP 3/3



KNOSP 0/3 **KNOSP ¼** **KNOSP 4/0**

Figure 3. Examples of the application of the Knosp scale in pituitary tumors (Knosp gradation right/ left).
(personal collection of Dr. V. Gh. Ciubotaru)

7. Differential diagnosis of pituitary adenoma

The differential diagnosis of pituitary adenomas, obtained by imaging, clinical and laboratory methods, is made with other types of pituitary tumors, as well as with other categories of saddle and / or perisellar lesions, tumor or non-tumor.

Among them, the primary lesions of the posterior lobe of the pituitary gland are very rare. **Secondary, metastatic lesions,** especially those originating in the breast, thyroid, lung and prostate, occur mainly in the posterior lobe and pituitary stem, frequently causing bone destruction of the sella turcica.

Craniopharyngiomas are the main type of tumors with which the differential diagnosis of pituitary adenomas is made, especially in children. Although they have suprasellar origin, 50% of them extend into the Turkish saddle, having an imagistic aspect of heterogeneous lesion, with both cystic and solid component, both fixing intensely the contrast substance; calcifications are common.

The meningiomas of the sella region are distinguished by rapid and intense fixation of the contrast substance, hyperostosis at the implantation site, as well as by compression of the carotid artery in the situation of invasion of the cavernous sinus.

Chordomas are notochord tumors originating from the primitive, with imaging of lytic lesions, nodules, heterogeneous, hyperintense on

T2, gadolinium fixing intense. Lymphocytic pituitary is a rare autoimmune disease that affects the pituitary gland and brainstem that appear thickened, intensely fixing the contrast substance.

8. Multimodal treatment of hypophyseal tumors

The treatment of symptomatic pituitary tumors aims at ablation of the tumor mass, decompression of the optic pathways, normalization of hormonal secretion, both in terms of hypersecretion and insufficiency of certain hormonal axes, obtaining histopathological details on the tumor, avoiding tumor recurrences. At the same time, it is considered to preserve the tissue and function of the normal pituitary gland, as well as to avoid potential complications. In the case of asymptomatic pituitary tumors, discovered incidentally, the attitude of imaging follow-up and endocrinological monitoring is considered to be more appropriate.

The current treatment of pituitary tumors is performed **multimodally**, for most of the tumors the surgical treatment is of choice, and the medical treatment, radiotherapy and chemotherapy are considered adjuvant treatments.

8.1. Surgical treatment

The basic principles of surgical indication in pituitary tumors (except prolactinomas) recommend **surgical resection as the treatment of choice** in active endocrine tumors, inactive endocrine tumors accompanied by mass effect by compression and / or infiltration of neighboring structures, and in tumors. Accompanied by pituitary insufficiency or in those whose progression over time is documented with imaging data.

Currently, the trend, supported by favorable long-term results, is to widen the indications for surgery, as a first-line treatment, for microprolactinomas. On the other hand, the other trend, replacement of surgery with medical therapy, such as in certain cases of acromegaly. Pituitary apoplexy accompanied by rapid deterioration of vision or paralysis of cranial nerves is a neurosurgical emergency (figure 4). Contraindications for resection are pituitary tumors associated with severe systemic disorders.

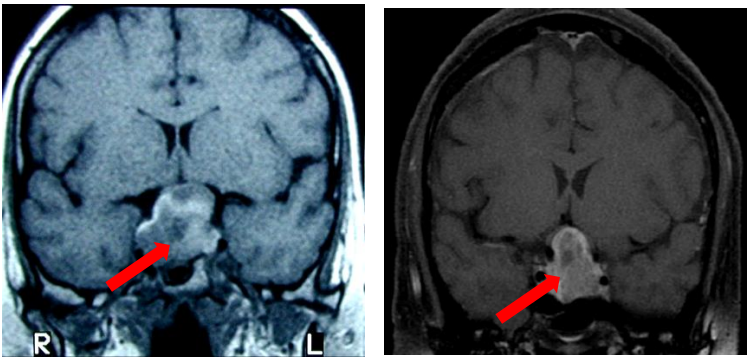


Figure 4. Pituitary apoplexy in two cases of pituitary macroadenomas. The T1 sequences with contrast substance highlight the large size of the tumors, the inhomogeneous appearance with areas of hemorrhage, necrosis and intratumoral cysts, the compression exerted on the optical pathways. (personal collection of Dr.V.Gh.Ciubotaru)

Surgery for pituitary adenomas, lesions of relatively small size, located extracerebral and even outside the conventional limits of the base of the skull, stimulated the surgeons to imagine and perfect the transsphenoidal approach, currently used to address other lesions of the saddle and perisellar region. Through the microsurgical transsphenoidal approach, more than 90% of pituitary tumors can be resected, but throughout history, it has disputed its primacy with transcranial approaches, still used today, but in a much smaller proportion. To the end, transsphenoidal approach offers the advantages of reduced operating time, the morbidity and mortality.

In the case of asymmetric supra- and lateral-lateral tumors, the transsphenoidal approach and the transcranial approach can be used independently or combined at short intervals for the purpose of complete tumor resection. Transsphenoidal endoscopic approach developed practically since 1990, reduced complications of nasal trauma and thus increase patient comfort, but prolongs the operation time, provides single panoramic view, but a two-dimensional field operator (operating field on the screen shown).

Transsphenoidal approach

The transsphenoidal approach is indicated in all cases of intrasellar

pituitary tumors, as well as in those with suprasellar extension, in which there is a wide communication between the intra and suprasellar portion, being contraindicated in cases where an aneurysm coexists in the saddle, the tumor has major extension average cranial fossa, or sphenoid sinus is not pneumatized, in which case a contraindication is relative. (11)(12)

a. Endoscopic transsphenoidal approach

Transsphenoidal endoscopic approach is defined as the technique that addresses sellar region transnasal transsphenoidal using the endoscope, excluding the microscope and/or any retractor (speculum) (Figure 5). The endoscopic transnasal approach has as a major indication reintervention on tumor remnants or recurrences (16).

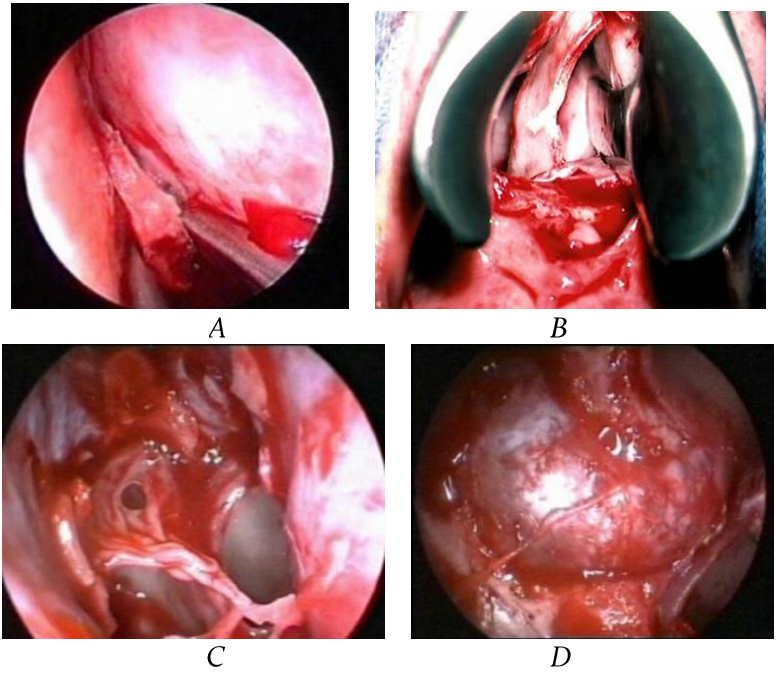


Figure 5: Transsphenoidal approach: nasal time (A. Endoscopic transsphenoidal approach; B. Microsurgical transsphenoidal approach), C. sphenoid time, D. saddle time
(Personal collection of Dr. V. Gh. Ciubotaru)

b. Transcranial approaches

Pituitary tumors that are indicated for transcranial approach are those that have a dominant extrasellar portion, asymmetrical extension in the anterior, middle or posterior cranial fossa, in which there is no wide communication between the intra and suprasellar portion, and the Turkish saddle is obviously not enlarged, as well as those that coexist with aneurysms or other malformations of the carotid artery or of the anterior cerebral artery, or are hard, fibrous. The most used transcranial approaches are basal approaches.

b.1. Basal approaches

The standard basal approaches used in resection of pituitary tumors are pterional, subfrontal and subtemporal, the choice of the most appropriate way depending on the position of the optic chiasm in relation to the saddle tubercle.

Among the basal transcranial approaches, the most used is the basal pterional approach with resection of the sphenoid ridge, indicated, but not exclusively, in cases where the optic chiasm is positioned normally or is postfixed, respectively located posterior to the saddle tubercle. This approach provides the shortest route to the suprasellar region.

b.2. Upper approaches

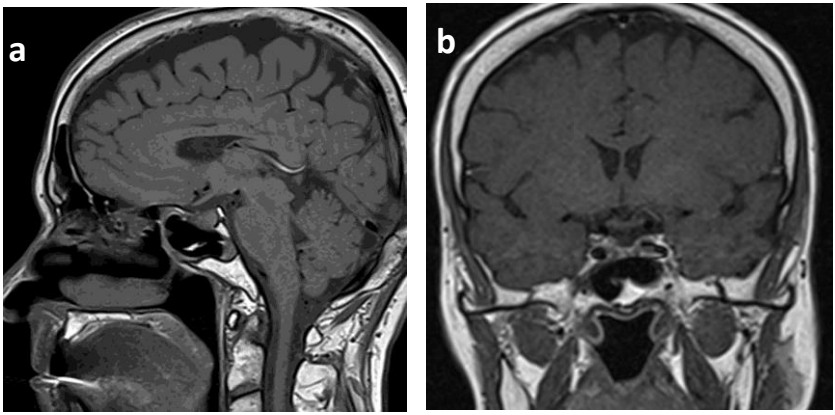
The superior approaches (transventricular or transcalos) are rarely indicated in pituitary tumors, namely in tumors with major extension at the level of the ventricle III. The transventricular approach is performed by a paramedian frontal craniotomy and the approach of the lateral ventricle by corticotomy at the level of the middle frontal gyrus. The tumor portion of the third ventricle is exposed by the Monro foramen.

9. Results of pituitary adenoma surgery

Pituitary adenoma surgery has multiple purposes, namely tumor resection as complete as possible, as well as the return of hormonal values to their physiological levels, obtaining biochemical cure or remission in case of secretory tumors or return to normal parameters of pituitary hormones, in case of pituitary insufficiency. Therefore,

postoperative follow-up is performed both by imaging control and by endocrine monitoring.

The quality of tumor resection is assessed both immediately postoperatively depending on the extension of the resection, and over time, by the frequency of recurrences. The percentage quantification of tumor resection is expressed as follows: total resection (100%), almost total resection (> 90%), subtotal resection (80-90%), partial resection (<80%) or biopsy (tumor fragments taken). The extension of pituitary tumors depends on many factors, among which we mention: tumor size, invasion in neighboring structures and especially in the cavernous sinus, use of preoperative medical treatment (somatostatin, bromocriptine), the surgeon's experience. The total and subtotal resection, globally appreciated on all types of pituitary tumors and approaches, amounts to 97%. Tumor recurrences occur in 10-20% of cases (13) (Figure 6)



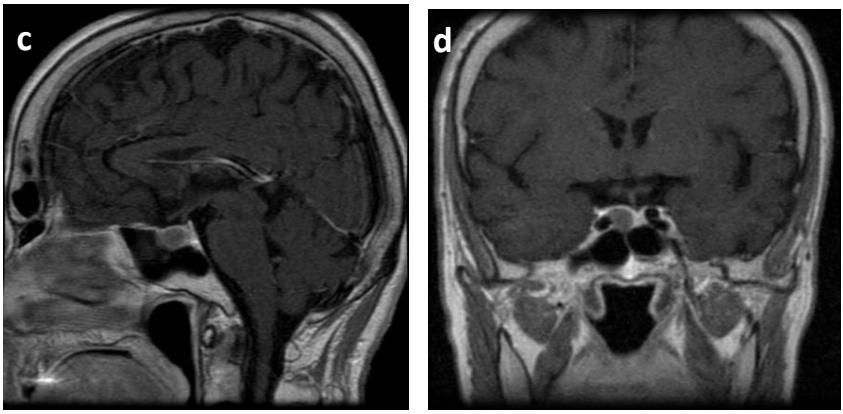


Figure 6. Transsphenoidally operated GH-secreting pituitary adenoma (total resection): preoperative aspect (a, b), postoperative aspect (c, d). (personal collection of Dr.V.Gh.Ciubotaru)

In cases with preoperative pituitary insufficiency, the normalization of hormone secretion is recorded postoperatively in 10-15% of patients, being more common when only one axis is affected, but being unlikely in the case of panhypophyseal insufficiency. Postoperative hormonal deficiencies are more common after transcranial approaches. The amelioration of the various visual defects is obtained in 80% of the cases operated transsphenoidally and 48% of the cases operated transcranially (13).

10. Complications of hypophysis tumor surgery

From the point of view of postoperative complications, transsphenoidal approach is significantly detached by the transcranial by a much lower frequency of occurrence. The mortality during the first month after surgery is estimated at less than 1% of the cases addressed transsphenoidal, compared with 2.3% of those operated transcranial (14).

The most common complications of the **transsphenoidal approach** are the following: nasal CSF fistula, which requires reintervention in less than 1% of cases ; meningitis and other intracranial infections (less than 1% of cases); visual defects caused

mainly by postoperative intracapsular bleeding, less often by direct damage to the chiasm, optic nerves or oculomotor nerves (1-2% of cases); severe vascular lesions (exceptionally rare); transient diabetes insipidus, found in 5-18% of patients and permanent diabetes, present in 2-3% of cases; postoperative hormonal deficiencies, installed in 1.4% of patients undergoing surgery. Other times regarding the complications of the procedure, endoscopic approach implies anterior pituitary insufficiency in 3.1% of cases, diabetes insipidus in 2.5% of cases and anosmia in 2.1% of cases. (15)

To these, to the **transcranial approaches** are added the complications (hemorrhage, infection) related to the craniotomy itself. Postoperative complications adjacent to the manipulation of vascular-nervous structures are more common than in cases treated transsphenoidal. However, it should not be lost sight of the fact that the transcranial approach addresses selected cases with increased operative difficulty. Postoperative worsening of vision occurs in 22% of patients, respectively, transient diabetes insipidus in 34% and permanent diabetes in 3.2%. It is also possible for neurological deficits and hypothalamic disorders, as a result of vasospasm or vascular lesions, such as hyperthermia, progressive obesity, memory disorders, sleep-wake circadian rhythm disorders.

10.1. Radiotherapy treatment

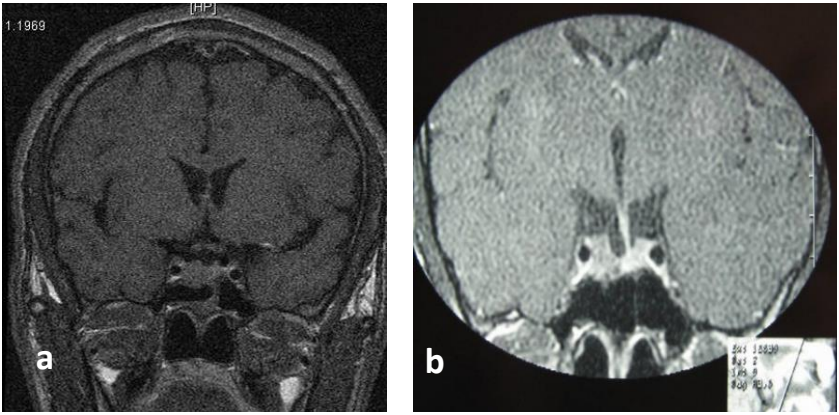
Radiotherapy is applied for the purpose tumor tissue destruction, but keeping the adjacent anatomical structures, in the present case, in particular to the optical paths and normal pituitary gland.

On pituitary tumors, the effect of radiotherapy is not installed immediately, requiring several months to obtain the effect of stopping tumor growth, this time increasing to years to produce an effective reduction in tumor volume and normalization of pathological hormonal hypersecretion. Therefore, radiation therapy is not indicated for first line, but only after surgical resection, except for patients with disease severe systemic, which contraindicate intervention of surgery.

Postsurgical resection radiotherapy is advisable in patients in which imaging investigations reveal the existence of tumor rest, especially if this has tended to rise or if hypersecretion pathological hormonal

persists. In the case of tumor remnants, radiotherapy is indicated after careful re-evaluation of the possibility of surgical reoperation. In the case of tumor recurrences, the first line indication is surgery and then radiotherapy. In prolactinomas, radiotherapy is recommended if the exhaustion of the possibilities of drug and surgical therapy has not led to the control of hypersecretion of prolactin.

Radiotherapy techniques have evolved significantly over the last 20 years, so that conventional fractional external radiotherapy is less and less used, giving way to techniques that precisely target the radiation beam to the tumor, namely radiotherapy using linear, conformational or stereotaxic accelerated particles. , single dose or fractional dose irradiation (LINAC, with the most advanced Cyber Knife variant) and stereotactic radiosurgery, gamma dose irradiation, applied in single dose (Gamma Knife). (figure 7)



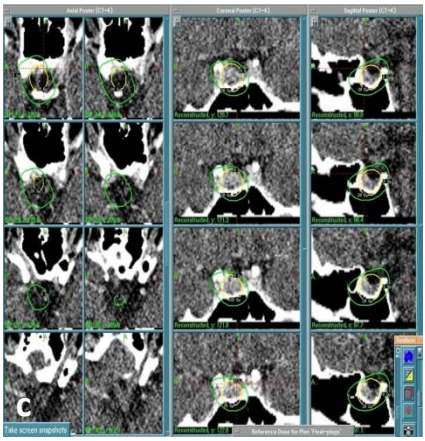


Figure 7. Operated and subsequently irradiated GH secreting adenoma Gamma Knife: a. Preoperative appearance; b. intracavernous tumor rest; c. irradiation planning.
(Personal collection of Dr.V.Gh.Ciubotaru)

10.2. Drug treatment

Preoperatively, pituitary insufficiency on the corticotropic and thyrotropic lines must be corrected in all cases, and hormone replacement continues in the early postoperative phase, because the eventual return to normal pituitary function occurs over time. Also, it is mandatory the systemic rebalancing to surgery, especially in patients with Cushing's disease, who have been systemic severely affected by the condition.

In the early postoperative period (first weeks) it is necessary to carefully monitor the function of the adeno and neurohypophysis (diuresis, serum and urinary electrolytes, cortisolemia), vision (visual acuity, visual field and oculomotor) and neurological status. Antibiotic prophylaxis is indicated in the first 24 h. Nasal tamponade is removed after 48 h.

Dexamethasone is administered **preoperatively**, but the adrenal axis is evaluated on the second or third day postoperatively by determining serum cortisol, values less than 10μg / L, requiring the administration of glucocorticoids (hydrocortisone). The definitive

evaluation of this axis is recommended at the end of the first postoperative week, simultaneously with the evaluation of the thyroid axis (6).

Diabetes insipidus, characterized by increased plasma osmolarity (hypernatremia), accompanied by a feeling of thirst or, less frequently, with normal fluid intake and increased diuresis, usually occurs in the first 48 hours; usually, remission and subsequent reappearance according to a three-phase model suggests its permanence. Diabetes insipidus is treated with injectable vasopressin, intravenously or orally. The syndrome of inadequate secretion of retrohypophyseal antidiuretic hormone (SIADH) leads to hyponatremia and is clinically characterized by headache, vomiting, altered consciousness and generalized seizures, which require water restriction, diuretics and intravenous sodium administration.

In the late postoperative phase, at 3 months postoperatively, the insufficiency of pituitary secretion is stable, its evaluation requiring in addition to basal hormonal values and stimulation tests, described in the chapter on preoperative endocrinological evaluation. Regarding the evaluation of biochemical remission, postoperative evaluation protocols must include: dosing of urinary free cortisol / 24 h and plasma ACTH in Cushing's disease, serum prolactin in prolactinomas, IGF1 and GH in the oral glucose suppression test in acromegaly.

11. Conclusions

Pituitary tumors are extracerebral tumors, mostly benign, which have a significant incidence in intracranial tumors. Although they most often have an obvious clinical expression, their diagnosis is usually made late. Surgery is the treatment of choice of these, with the exception of prolactinoma, which is the drug of first choice treatment. (16) The surgical treatment aims mainly at the ablation of the tumor mass, the decompression of the optical pathways and the normalization of the hormonal secretion. The transsphenoidal approach, when possible, is the optimal surgical solution, being one of the most effective and our neurosurgical approaches. Its use requires compliance with the principle of surgeons to delicately maintain structural integrity vascular - nerve and hemostasis. Radiotherapy, endocrinological drug therapy

and chemotherapy are complementary therapeutic solutions in the treatment of pituitary tumors. These tumors have in most cases a favorable prognosis.

Abbreviations

ACTH- adrenocorticotropic hormone; **CRH**- corticotropic stimulating hormone, corticoliberin; **CT**- computed tomography; **FSH**- folliculinostimulating hormone; **GH**- growth hormone, somatotropic hormone; **GnRH**- gonadotropin-releasing hormone, gonadoliberin; **IGF1**- somatomedin C; **CSF** - cerebrospinal fluid; **LH**- luteinizing hormone; **Men**- neoplasia multiple endocrine; **PRL**- prolactin; **MRI** - Imaging MRI; **T3**- triiodothyronine (thyroxine); **T4**- tetraiodothyronine (thyroxine); **TRH**- thyrotropin-releasing hormone, thyroliberin; **TSH**- thyroid hormone

Disclaimer: The authors declare no conflict of interest in realizing the material.

References:

1. Chin SO. Epidemiology of Functioning Pituitary Adenomas. Endocrinol Metab (Seoul). 2020;35(2):237-242.
2. Thapar K, Kovacz K, Horvath E, Asa SL - Classification and pathology of pituitary tumors . In: Wilkins RH; Rengachary SS (ed) Neurosurgery, ed.2, New York: McGraw-Hill 1996: 1273-1289
3. Constantinovici Al Ciubotaru V Ogrezeanu I . Principles of diagnosis and treatment in pituitary tumors . In: Treatise on Surgery Surgery (Popescu I, Ciurea AV). Romanian Academy Publishing House , Bucharest, 2007; (2): 256-266
4. Maartens NF - The history of the treatment of pituitary adenomas . Endocrine, Oct 2005; 28 (1): 9-26
5. Vandeva S, Jaffrain-Rea ML, Daly AF, Tichomirowa M, Zacharieva S, Beckers A. The genetics of pituitary adenomas. Best Pract Res Clin Endocrinol Metab. 2010; 24(3):461-76.
6. Lloyd RV, Kovacy K, Young WF Jr, and dust .- WHO Classification of Tumors of the endocrine organs . In: De Lellis et al (ed.), IARC Press: Lyon, France, 2004

7. Molitch ME. Diagnosis and Treatment of Pituitary Adenomas: A Review. JAMA. 2017; 317(5):516-524.
8. Drummond J, Roncaroli F, Grossman AB, Korbonits M. Clinical and Pathological Aspects of Silent Pituitary Adenomas. J Clin Endocrinol Metab. 2019; 104(7):2473-2489
9. Lake MG, Krook LS, Cruz SV. Pituitary adenomas: an overview. Am Fam Physician. 2013; 88(5):319-27.
10. Knosp E, Steiner E, Kitz K, Matula C - Pituitary adenomas with invasion of the cvaernous sinus space: a magnetic resonance imaging classification compared with surgical findings . Neurosurg, 1993; 33 (4): 610-618
11. Buchfelder M- Treatment of pituitary tumors . Endocrine, Oct 2005; 2 8 (1): 67-75
12. Zhang H, Zhang X, Du H, et al. Microsurgical resection of pituitary adenoma via single-nostril transsphenoidal approach. Clin. Oncol. Cancer Res. 2009; 6:446–450.
13. Buchfelder M, Kreutzer J-Transcranial surgery for pituitary adenomas. Pituitary, 2008; 11: 353-360
14. C IRIC I Ragin A, Baumgartner C, et al.- Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience. Neurosurg, 1997; 40: 225-237
15. Paluzzi A, Fernandez-Miranda JC, Tonya Stefko S, Challinor S, Snyderman CH, Gardner PA. Endoscopic endonasal approach for pituitary adenomas: a series of 555 patients. Pituitary. 2014 Aug;17(4):307-19.
16. Ogrezeanu I, Ciubotaru V.Gh., Constantinovici A, Diagnosis and multimodal treatment of pituitary adenomas, Treatise on Neurosurgery vol I, Ed.Medicala 2010, 609-631.

BRAIN STEM TUMORS

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When you are young you strive to obtain all that you wish for. Later, you are content with wishing for things you can obtain. This attitude has the advantage of buying you more time.
Jerome K. Jerome, English writer (1859-1927)

Contents

1. General data. History

Until recently, brainstem tumors were considered unresectable, inoperable lesions, constituting one of the most difficult pathologies to treat in pediatric age. Advances in the field of neuroimaging (CT, MRI), sophisticated techniques of neurophysiological monitoring, improvement of microsurgery techniques have made a significant contribution in the surgical treatment of these lesions.

Brainstem gliomas are recognized to be a heterogeneous group of tumors, classified by MRI into several categories depending on how they evolve, location, longitudinal enlargement, focal or diffuse growth, contrast, presence or absence of hydrocephalus, cysts, hemorrhage or necrosis, of the degree of surgical resectability, respectively the general prognosis. (1)

The prognosis is more unfavorable than the mesencephalic and bulbar ones, the prognosis being all the more reserved as the tumor formation has a more infiltrative character.

Brainstem gliomas represent approximately 10% of brain tumors in pediatric age, ranking in the top 3; they can be found at any age, although they mainly appear in pediatric age, with a peak incidence at the time of diagnosis, between 7 and 9 years; there are no significant differences in the sex of the patients.

2. Epidemiology

Trunk gliomas represent 10-20% of pediatric neoplasms, respectively 1-2% of adult brain tumors, in about 75% of patients manifesting before the age of 20 years. The highest incidence is found in the last half of the first decade of life (the peak incidence is between 7-9 years), without a noticeable difference between the sexes. (2) Most of these cases are sporadic but there have been cases. family.

3. Classification

In the last decade, as a result of advances in neuroradiology, it has been possible to define a greater heterogeneity of brainstem gliomas. MRI is the method of choice in the investigation and classification of brainstem tumors. Astrocytomas are the most common intrinsic

tumors of the brainstem, histologically being fibrillar, in contrast to cerebellar astrocytomas that are predominantly pilocytic.

Other tumors that can develop in the brainstem are PNET, lymphomas, ganglioglyomas, and oligodendrogiomas or even metastases. Lymphomas are distinguished by uniform contrast uptake compared to astrocytomas. Ependymomas, although usually developing from the floor of the IV ventricle, occupying the entire ventricle or extending into the pontocerebellar angle, can sometimes mimic an intrinsic brainstem tumor by compression or even insinuation at its level.

A variety of classification schemes have been used over the years. Initially, these were based on brain CT scans and intraoperative observations; subsequently due to the reliability of the images obtained by MRI, these classification schemes became more and more complex, subdividing the trunk tumors according to location, epicenter (diffuse, focal), the presence or not of hydrocephalus or hemorrhage and the way of tumor expansion.

Jallo et al. took into account, in trying to classify these tumors, CT and MRI imaging as well as those obtained intraoperatively, dividing the brainstem tumors into: diffuse, focal (circumscribed tumor masses less than 2 cm, without perilesional edema), and cervicobulbar.

Barkovich et al. in 1991 they suggested a classification of these tumors in relation to:

a) location: midbrain, pons, bulb

b) focality: diffuse or focal

c) tumor growth direction and extension

d) the degree of widening, of ballooning of the brainstem

e) exophytic component

f) the presence of hemorrhage or necrosis

g) evidence of hydrocephalus.

A more recent and often used classification is that of Choux et al., 1999 (CT, MRI) (5):

- **Type I:** intrinsic, diffuse tumors, hypodense on CT, hypointense in T1-MRI, without significant contrast capture.
- **Type II:** intrinsic and focal tumors, which may be solid or cystic.
- **Type III:** exophytic tumors, both dorsal and lateral.

- **Type IV:** cervical-bulbar tumors.

Diffuse brainstem gliomas are the most common tumors of the brainstem, accounting for about 60-75% of all neoplasms. They are generally over 2 cm in size. at the time of presentation and are characterized by diffuse infiltration and trunk ballooning. The epicenter of these lesions is usually located in the pons, but the rostral or caudal extensions are not uncommon. (13) On MRI sequences in T1 they appear as hypointense, with irregular edges suggesting the infiltrative nature of these lesions. In T2, diffuse brainstem gliomas, unlike focal ones, are discreetly hyperintense, with gadolinium uptake being variable and without prognostic involvement.

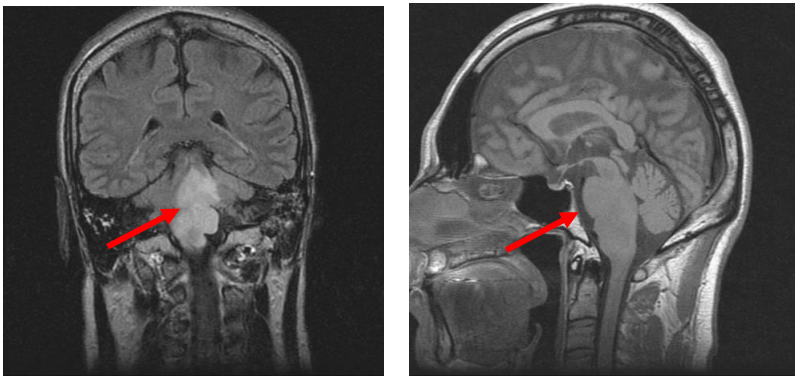

Figure 1. MRI examination of a case of diffuse brainstem glioma (personal collection of Prof. Dr. Stefan Ioan Florian)

Diffuse gliomas are commonly malignant fibrillar astrocytomas (grades III, IV). The specificity of MRI diagnosis of diffuse brainstem gliomas has been studied by Albright et al. In 1993 (12), they concluded that most diagnostic biopsies do not work, due to the fact that MRI provides a diagnosis with high specificity in the case of diffuse gliomas.

Focal gliomas are defined as small, well-circumscribed lesions located in both the mesencephalon and the bridge or bulb. They may be solid or cystic and always have a distinct demarcation margin from normal brain tissue on MRI; the cystic component can be large compared to the solid component. It has a low degree of infiltration and

perilesional edema and the contrast uptake is variable; however, a uniform contrast is suggestive of a juvenile pilocytic astrocytoma. These tumors are often benign, grade I and II astrocytomas.

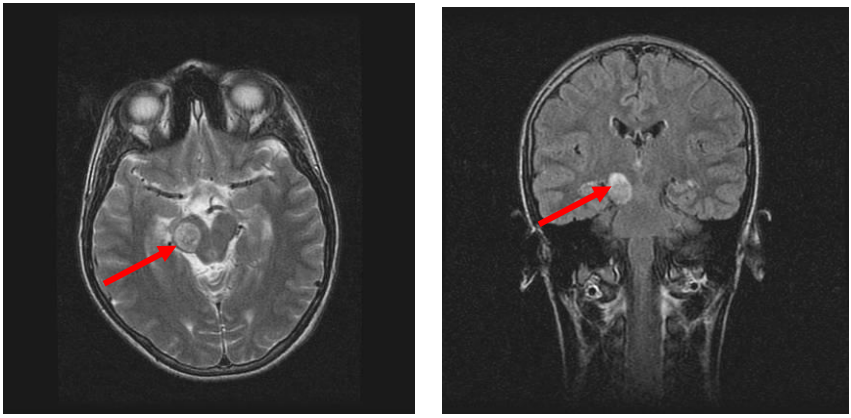

Figure 2. Axial and coronal incidence NMR appearance of a focal mesencephalic glioma
(Personal collection of Prof. Dr. Stefan Ioan Florian)

Dorsal exophytic tumors are a group of tumors originating in the subependymal glial tissue; they are usually extended and arise from the floor area of the IV ventricle and generally fill the ventricle without invading the local cerebral substance; the exophytic portion of the tumor plunges into the IV ventricle, which explains the relatively late onset of symptoms in these patients. On MRI sequences, they appear as well-defined formations, hypointense in T1 and hyperintense in T2, contrasting with gadolinium administration, thus difficult to differentiate from ependymomas and choroid plexus papillomas. This group of tumors almost always consists of low-grade gliomas. According to Jallo and Calas, exophytic tumors that grow toward the lateral and ventral portions of the brainstem have a higher degree of malignancy compared to tumors that project into the IV ventricle. (11)

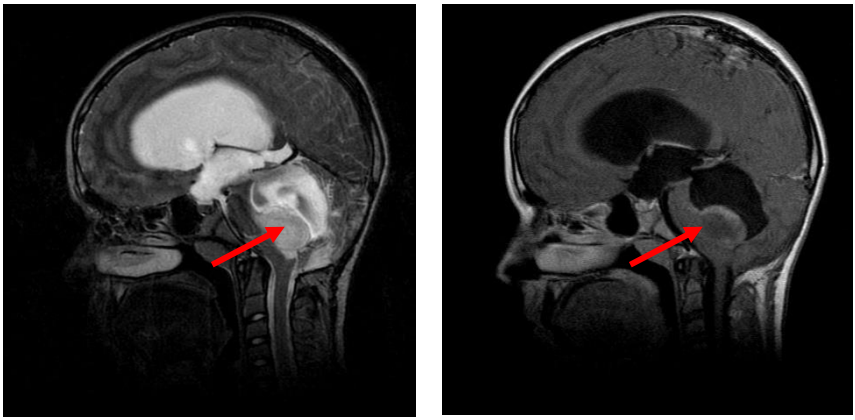

Figure 3. Native (T2 left) and contrast (right) MRI examination in a case of exophytic brainstem tumor projected into the IV ventricle (Personal collection of Prof. Dr. Stefan Ioan Florian)

Cervicobulbar tumors are somewhat similar to intramedullary spinal gliomas, with the epicenter of these tumors being located in both the bulb and the superior cervical marrow.

On MRI sequences, these tumors appear as lesions with a mixed hypo / isointense signal, and the presence of cysts or associated syringomyelia cavities can also be identified.

Most are represented by low-grade astrocytomas, with low infiltration capacity, their rostral extension being limited by the decussation of the corticospinal tract and the medial lemniscus; only high-grade astrocytomas have the ability to extend to the cranial.

The rostral tumor mass is previously limited by the pyramidal decussation, so that the tumor extends posteriorly to the obex, and can enter the IV ventricle. Therefore, these small-grade tumors have an exophytic appearance, displacing the rostral bulb, while the upper cervical marrow acquires a ballooned appearance.

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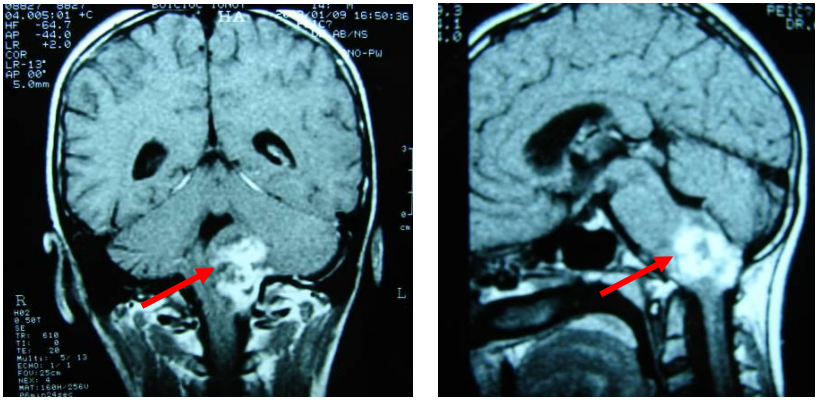

Figure 4. MRI examination with contrast in coronal and sagittal in a case of cervico-bulbar tumor; the inhomogeneous contrast and moderate exophytic appearance of the tumor should be noted (Personal collection of Prof. Dr. Stefan Ioan Florian)

4. Pathology

Brainstem gliomas present in 75% of cases in the form of diffuse lesions, the rest being intrinsic focal lesions of the trunk; the latter may or may not have an exophytic component with a starting point from the dorsal portion of the bridge, towards the IV ventricle, from the tectal plate or from the central portion of the mesencephalon or bridge in the

prepontine or premezencephalic cisterns. They develop along pre-existing structures, bundles of nerve fibers and the pial membrane causing little tissue damage, and grow both longitudinally and axially; it develops with predilection on the left side of the brainstem; they can invade neighboring structures, the cervical marrow, the cerebellar hemispheres, or they can plunge into the IV ventricle, subsequently causing obstructive hydrocephalus.

Small-grade tumors tend to grow in the upper half of the trunk, while high-grade gliomas have a predisposition to appear in the lower half. Hydrocephalus usually develops late in the course of the disease, with the exception of patients whose tumors are located periapeductally, tectally.

Morbidity is due to the compression exerted by these tumors on the neighboring neurovascular structures, through the tumor itself, hemorrhage or edema. The presentation of these tumors varies with their location, which is predictive of prognosis:

- tectal - pilocytic gliomas, focal, with variable contrast uptake, may or may not have calcifications.
- mesencephalic tegmentum - focal, pilocytic: tumor node associated with a cyst;
- diffuse pontine - noncaptive, diffuse or fibrillar. (7)

5. Clinical data

Brainstem gliomas often have an insidious onset and are clinically manifested by gait disorders and cranial nerve syndromes, diplopia, focal motor deficits, headache, vomiting, paresthesia and facial paresis, tinnitus, vertigo.

Walking disorders are due to damage to the cerebellar pathways or the pyramidal tract. Focal walls, a sign of damage to the pyramidal tract, can be unilateral or bilateral. Symptoms due to hydrocephalus occur in tumors of the mesencephalic tegmentum that cause stenosis of the Sylvius aqueduct.

Headache associated with trunk tumors is the expression of obstruction of the IV aqueduct or ventricle by dorsal expansion, traction of the surrounding meninges or basilar artery.

Dorsal mesencephalic gliomas may manifest as diplopia, internuclear ophthalmoplegia indicating interest in the medial longitudinal bundle; may cause Parinaud syndrome with pupillary disorders, paresis of vertical gaze and accommodation, convergent nystagmus, eyelid retraction.

Cervicobulbar tumors are usually manifested by dysphagia, gait disorders, nasal speech, vomiting, and muscle weakness; we often find painful accusations nuchal, torticollis, the presence of the sign Lhermitte. Sensitivity disorders in the face are the expression of trigeminal nucleus damage, while dysphagia / dysphonia occur as a result of involvement of the lower cranial nerves IX, X. Ocular myoclonus and "downbeat" nystagmus are often found in case of bulb injury. (7)

At the time of diagnosis, the most common neurological signs include nerve paresis VII, VI, often horizontal nystagmus, cerebellar signs, motor deficits, hyperreflexia, and Babinski sign.

6. Paraclinical investigations

MRI is also in these cases the procedure of choice in the diagnosis of brainstem tumors and in their modern classification. It is useful in visualizing vascular malformations and other tumor processes that have escaped CT investigation. The typical appearance on MRI is that of an infiltrative tumor mass that widens the brainstem, hypo or isointense in T1-weighted images and with hyperintense heterogeneous signal in T2, with variable contrast uptake. MRI allows the evidence of infiltration of leptomeninges and neighboring neurovascular structures. Low-grade brainstem tumors do not contrast after gadolinium administration. In the case of mesencephalic tumors, especially those originating in the tectum, the typical appearance is of hypointense lesion in T1 and hyperintense in T2, noncaptive; the contrast of such a tectal lesion, especially in adults, raises the suspicion of a metastasis, especially in the case of a history of systemic cancer in the past. On post-mortem examination, the trunk gliomas have little edema, the abnormalities visualized in the T2 sequences reflecting the spatial extension of the tumor. High-grade tumors show contrast and signs of necrosis or hemorrhage.

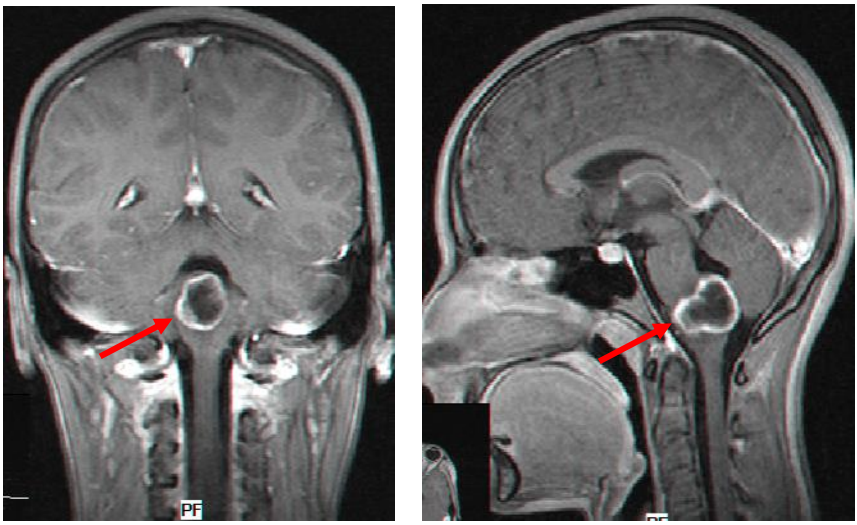

Figure 5. MRI examination in coronal and sagittal section of a bulbo-pontine infiltrative glioma
(Personal collection of Prof. Dr. Stefan Ioan Florian)

The CT scan of the brain finds its usefulness in assessing the different degrees of hydrocephalus secondary to the tumor process of the brainstem. In contrast, small focal lesions that do not deform the IV ventricle as well as exophytic tumors in the basal cisterns may remain undetectable (bone overlap and artifacts at the craniospinal junction). Usually, on CT examinations, the trunk gliomas appear to be hypointense or isointense and do not catch the contrast, the calcifications being found in a small number of cases. Intratumoral cystic changes as well as the degree of displacement of the ventricular system can also be visualized.

Cerebral arteriography (4 vessels) is useful in differentiating vascular lesions, including tumors (hemangioblastoma), from gliomas.

The potentials evoked by the trunk can find their utility during the surgery, for monitoring its function and evaluating the involvement of the nerves VII, VIII.

7. Differential diagnosis

The differential diagnosis of infiltrative lesions of the brainstem is limited to several diseases: ependymomas, medulloblastomas, medullary epithelium, metastatic dissemination, hemangioblastoma, arteriovenous malformations.

Multiple sclerosis is difficult to differentiate from trunk gliomas due to the mode of onset and clinical manifestation, similar to them, in elucidating the diagnosis an important role is the study of somatosensory or visual evoked potentials, MRI examination and CSF examination.

8. Treatment

The treatment of brainstem tumors is a real challenge even for an experienced neurosurgeon. At present, the benefit of new therapies has not been shown to be noticeable compared to conventional treatment and radiation therapy.

Symptomatic treatment

Patients who develop hydrocephalus due to aqueduct obstruction have as initial treatment options the initial administration of corticosteroids, followed by ventriculostomy or the establishment of a ventriculoperitoneal drainage in order to improve symptoms and reduce the risk of cerebral engagement. (8)

Surgical treatment

Rigorous selection of patients is a fundamental principle underlying success in brainstem neoplasm surgery. The way of clinical presentation, the imaging aspects and the classification of the tumors are useful in establishing the optimal surgical treatment.

The vast majority of trunk tumors are diffuse pontine gliomas, which do not require stereotaxic biopsy and are not surgically resectable. It is important to differentiate between tumors that are unlikely to respond to treatment and those that do not require surgical treatment.

Some focal lesions, such as intrinsic tectonic gliomas, have no indication for open surgery; can be observed clinico-imaging and in case

of progressive neurological degradation by decompensation of obstructive hydrocephalus ventriculocisternostomy or ventriculo-peritoneal drainage is performed. It should be borne in mind that a brutal decompression of the ventricular system during shunting risks the ascending engagement of the cerebellar hemispheres and the trunk. (9)

Surgical treatment is indicated in case of:

- intraaxial cervicobulbar tumors,
- Tumors with a cystic component
- Tumors with exophytic component.

In these cases, early surgery is the first intention, before significant deterioration of neurological status and the administration of any other type of treatment, radio or chemotherapy. The purpose of the surgery is to reduce the tumor volume, to obtain a tumor fragment for histopathological examination and to restore the CSF circulation, without causing the installation of serious neurological complications. The success of the surgery and the final postoperative outcome are equally dependent on the biological nature of the tumor. (10)

The surgical approach

As previously mentioned, the choice of approach depends on the location of the tumor. Although most tumors located superior to the midbrain are conservatively treated by CSF delivery, in some cases, rapid tumor progression requires its approach by open surgery.

In the case of dorsal mesencephalic tumors, the generally accepted approach is the supracerebellar infratentorial one (figure 6). This approach provides direct access to the midbrain without the interposition of brain tissue; the deep venous drainage system including v. Galen and v. internal cerebral is usually located above the tumor and can thus be easily protected. The limitation of this approach is too sharp an angle of the tentorium, observable on the NMR sequences.

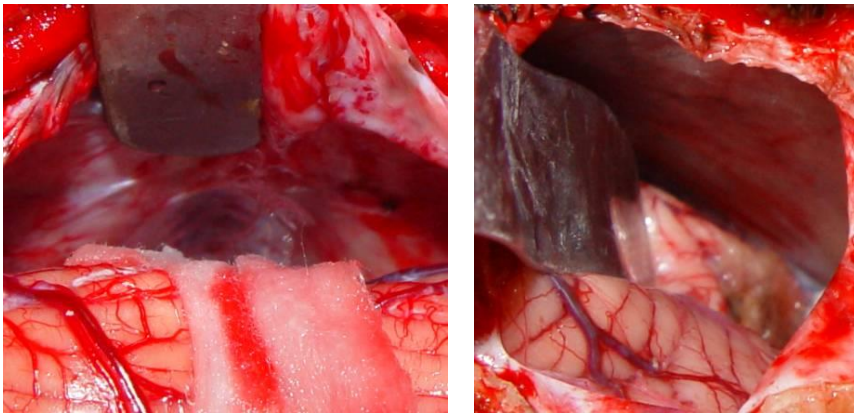

Figure 6. Introperative aspect in a median infratentorial supracerebellar approach (left image), respectively lateral supracerebellar (right image) (Personal collection of Prof. Dr. Stefan Ioan Florian)

For lesions located ventromedially at the level of the mesencephalon, in the vicinity of the interpeduncular cisterns, the indicated approach is the pterional one, while tumors located locally ventrally are desirable to be approached subtemporally by sectioning the incision of the tentorium. (11)

Pontine or bulbar dorsal exophytic gliomas may undergo radical surgical excision due to their histological benignity and intrinsic tumor growth characteristics; they were the first type of trunk gliomas for which radical surgical resection was attempted. (figures 7 and 8).

The approach of these tumors is preferably done by midline suboccipital craniotomy in children, respectively suboccipital craniectomy in adults. One of the most important aspects in these cases is the progressive resection ("peace meal") of the tumor while the floor of the IV ventricle is kept in sight to limit any injury to the parenchyma of the brainstem. (10)

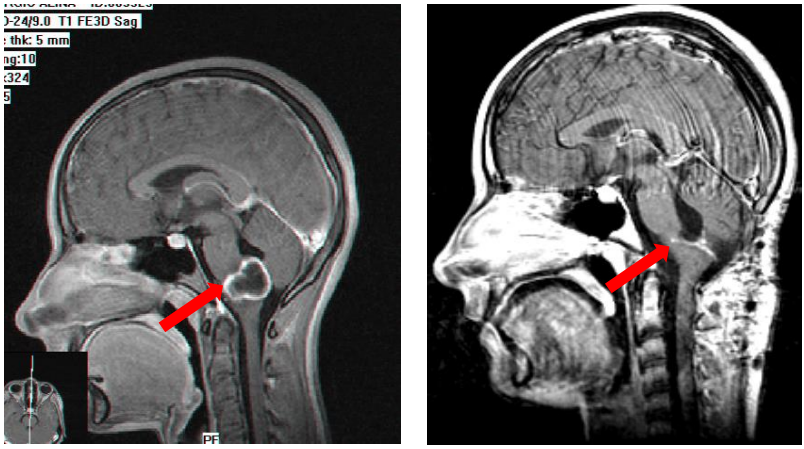

Figure 7. MRI examination with pre- and postoperative contrast of a bulbo-pontine exophytic glioma projected in the IV ventricle (Personal collection of Prof. Dr. Stefan Ioan Florian)

Regarding the intrinsic focal tumors, their surgical resection is attempted only after the identification of the floor of the IV ventricle and the mapping of the safe access corridors. Gliomas located on the ventral face of the bridge and extended to the pontocerebellar angle can be ablated by lateral retrosigmoid approach, with great care not to damage the tracts of nerves V, VII, VIII, bulb and nerves IX and X.

Cervicobulbar gliomas also benefit from radical surgical treatment by midline suboccipital approach associated with opening of the magnum foramen and resection of the C1 posterior arch, possibly C2-C3 laminectomy, depending on the caudal extension of the tumor; Excessive, multilevel laminectomy is to be avoided, especially in children, due to the spinal deformities that may occur, in which case an osteoplastic laminectomy is attempted. The tumor extends superiorly limited by the pyramidal decussation, then posteriorly, causing the expansion of the dorsal face of the bulb and the invasion of the IV ventricle; almost invariably its location is superficial, subpial.

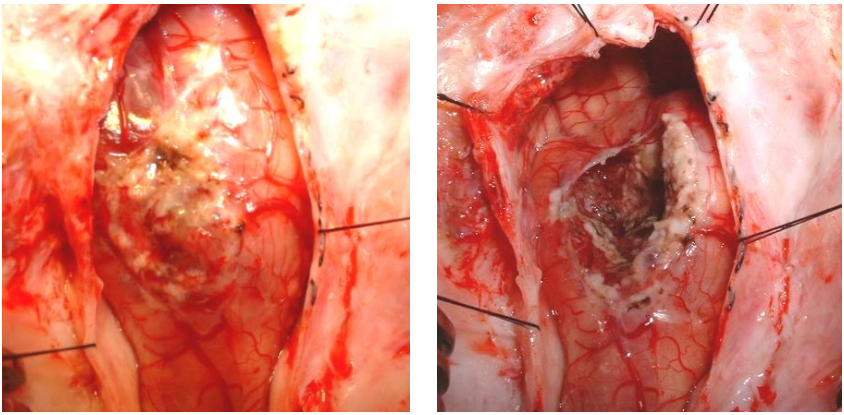

Figure 8. Introperative aspect in a recurrent exophytic glioma (at the first intervention pilocytic astrocytoma, at the second anaplastic astrocytoma) bulbar, subtotal resection
(Personal collection of Prof. Dr. Stefan Ioan Florian)

Tumor resection

In most operated cases, the tumors could be resected by a thorough microsurgical dissection, gentle aspiration and progressive mechanical reduction, without excessive use of electrocoagulation or ultrasonic aspirator (which is not even available in our service). Practically, where the incision is necessary, we use the scalpel to produce a linear lesion, in an area located above the most superficial point of the tumor and as avascular as possible. The length of the incision should not exceed 1-1.5 cm, which provides a sufficient opening for tumor resection. (10) We avoid the use of bipolar coagulation, and when necessary, use the current with the lowest frequency that causes coagulation of the peri or intratumoral vessel. The creation of the cleavage plan is performed, after the identification of the tumor, with the help of microdisection, the reduction being achieved progressively by delicate aspiration, the use of microsurgical scissors and microsurgical tumor forceps. The bleeding points are swabbed with small fragments of Surgicel, maintained for a few minutes and then extracted by washing. In focal tumors, the limit of tumor demarcation is usually visible, and maintaining this plan reduces the chances of lesions with devastating

neurological consequences. In cystic tumors, the evacuation of the cyst, possibly of a better represented portion of its wall, is sufficient to obtain the decompression of the trunk. Do not attempt to completely detach the cyst walls. All these maneuvers must be performed with maximum delicacy, any untimely gesture can have unpredictable consequences.

After resection of the tumor, a perfect hemostasis will be ensured. The occurrence of a postoperative hematoma in this region is usually equivalent to the loss of the patient.

A tight closure of the dura mater with periosteal plastic surgery will be performed to prevent the appearance of liquid fistulas, a complication that can jeopardize the surgical procedure.

Derivation of cerebrospinal fluid

In diffuse brainstem tumors as well as in mesencephalic tumors with a tendency to expand after the thalamus, the only surgical indication is the derivation of cerebrospinal fluid, in cases of obstructive hydrocephalus. Although ventricular-cisternostomy seems the most natural indication, which in addition avoids the patient's dependence on a mechanical drainage system (as happens in ventricular-peritoneal shunts), this intervention is not always possible.

Complications

Possible postoperative complications can lead to

- transient or permanent aggravation of pre-existing neurological deficits, by the appearance of a hematoma in the tumor bed, by vascular injuries (PICA, vertebral a., transverse sinus) with the development of extensive ischemia in the corresponding territories, or damage to the normal functional brain parenchyma.

- cerebellar signs (nystagmus, ataxia, asymmetry) by aggressive surgical procedures

- cranial nerve paresis is variable depending on the chosen approach; bridge-level approaches can result in persistent diplopia by internuclear ophthalmoplegia; facial paresis by damaging the facial nerve nucleus can lead to significant cosmetic and sensorimotor dysfunctions; lower cranial nerve injuries, IX-XII, can result in severe dysphagia, respectively paralysis of the vocal cords and loss of swallowing reflexes and cough.

- cerebellar mutism which typically manifests itself between days 1-4 in patients who did not have any speech deficiency immediately postoperatively. (13) This is especially the case in cases where an extensive incision of the vermis was performed.

- other complications that may occur are those common in posterior fossa surgery:

- acute postoperative hydrocephalus due to cerebellar edema or obstruction of the physiological flow pathways of the CSF by blood products or tumor residue,

- pseudomeningocele with or without CSF fistula on the outside,

- local infections, meningitis

Stereotaxic biopsy

Stereotaxic biopsy aims to obtain a tissue diagnosis, resection of the exophytic portion, and drainage of the cystic cavity with the restoration of CSF drainage pathways. (10)

Radiotherapy

Radiotherapy is the therapeutic method of choice for most trunk gliomas with progressive neurological symptoms. Some adult patients with tectal, periapeductal or cervicobulbar lesions or with minimal neurological symptoms may be candidates for clinical-imaging observation, radiotherapy being reserved only for those with obvious signs of tumor progression. The response to radiation therapy and the dose of radiation depend on a number of variables, such as: tumor location, histological type and response to early treatment. It has been reported that patients with trunk gliomas with exophytic component responded better to radiotherapy compared to those whose tumors did not have exophytic components.

Chemotherapy

The efficacy of chemotherapy in children and adult patients with brainstem gliomas has not been proven.

prognosis

The detailed history of the disease and the way of clinical presentation are important elements in establishing the tumor histology and implicitly the general prognosis.

The prognosis is favorably influenced by: 1). Neurofibromatosis; 2). Symptoms present at least 12 months prior to positive diagnosis; 3). Exophytic forms; 4). clinical picture suggestive for tumor with low degree of malignancy; 5). Focal tectal or cervicobulbar tumors; 6). Presence of calcifications on CT scan (9).

9. Conclusions

Brain tumors represent a category with wide heterogeneity both in terms of clinical and imaging presentation and applicable therapy. Therefore, adequate knowledge of the different types of tumors that may occur in this region, the possible natural evolution and the therapeutic armament that we currently have at our disposal is an essential condition for improving the prognosis of these patients.

Many of the cases with unfavorable post-therapeutic evolution have their main cause in not adapting the therapeutic attitude to the most appropriate one in the present case. From a surgical point of view, the essential condition is the careful selection of cases that can benefit from the surgical treatment available in that service and requesting a second opinion from a center with more experience in the field is a gesture of honesty and professional probity.

References:

1. Epstein FJ, Farmer JP. Brain-stem glioma growth patterns. J Neurosurg 1993; 78: 408–12
2. Packer RJ, Nicholson HS, Vezina LG, Johnson DL. Brainstem gliomas.Neurosurg Clin N Am 3: 863-879, 1992
3. Jallo GI, Biser-Rohrbaugh A, Freed D. Brainstem gliomas. Childs Nerv Syst. Mar 2004;20(3):143-53.
4. Barkovich AJ, Krischer J, Kun LE, et al. Brain stem gliomas: a classification system based on magnetic resonance imaging. Pediatr Neurosurg. 1990-91;16(2):73-83
5. Choux M, Lena G, Do L: Brainstem tumors, in Choux M, Di Rocco C, Hockley A (eds): Pediatric Neurosurgery.New York: Churchill Livingstone, 2000, pp 471-491

6. Jallo G, Kothbauer K, Epstein FJ: Surgical management of cervicomedullary and dorsally exophytic brain stem tumors. Operative Techniques Neurosurg. 2000, 3:131- 136
7. Ragheb J., Epstein FJ: The surgical classification and management of brainstem tumors in children, International Pediatrics vol.15, no.1/2000, p.15-20
8. Constantini S, Epstein F. **Surgical** indication and technical considerations in the management **of** benign brain stem gliomas. [Review]. J Neurooncol 1996; 28: 193–205
9. Bricolo A: Surgical management of intrinsic brain stem gliomas.Operative Techniques in Neurosurgery 3:137- 154, 2000
10. Florian St,Pintea BS, Tumorile de trunchi cerebral in Ciurea AV (Ed.) Tratat de neurochirurgie, Vol. 1, Ed. Medicala, 2010, pg. 577-590
11. Jallo GI., Freed D., Epstein FJ.: Current management of brainstem gliomas, Annals of Neurosurgery, 2003; 3(1): 1- 17.
12. Albright, AL.: Tumors of the pons, Neurosurg Clin N Am 4: 529- 536, 1993

INTRACRANIAL SCHWANNOMAS

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The life is short, the craft so long to learn
Hippocrates (460 BC – 370 BC)

Contents

1. Introduction

It is a benign tumor that develops from Schwann cells, most often the lesion being unique. In patients with Recklinghausen neurofibromatosis (type II) we can find multiple neurinomas (the most characteristic example is bilateral nerve injury VIII). The most common intracranial schwannomas are those that affect the cranial nerves VIII, V, VI, IX and X. (1,2)

From the anatomopathological points of view, 3 tumor types of schwannomas are described, according to their consistency:

- type I or Antoni A which is rough
- type II or Antoni B which is soft
- type III, with mixed characters.

2. Vestibular schwannoma (acoustic neurinoma)

Among neurinomas, the most common is acoustic neurinoma. It is also called vestibular schwannoma; it is an encapsulated benign tumor formed by differentiated Schwann cells. The frequency of intracranial neuromas is about 7.5-8%. These tumors are more common in patients with type II neurofibromatosis, between 40-60 years, in this particular pathological situation they are frequently bilateral. (15)

Vestibular schwannoma develops from the VIII pair of cranial nerves, at the level of the internal auditory canal (figure 11). There is a slow dimensional increase and the presence of only minor clinical signs (vertigo or hearing loss) in large tumors.

The Obersteiner-Redlich area (the 'border' between the central and peripheral nervous systems), the level at which the myelin sheath is replaced by Schwann cells, is where the tumor begins to develop. By size and relationship with the surrounding elements Sami & Co. established the following four evolutionary degrees. (3-5)

Samii classification of vestibular schwannomas (9,10)

I. strictly intracanal development (in the internal auditory canal)

II. the tumor exceeds CAI

III. a. the tumor develops in the cistern of the pontocerebellar angle

III. b. the tumor develops in the cistern of the pontocerebellar angle, comes into contact with the brainstem, but without compressive phenomena

IV. a. tumor compresses the brainstem

IV. b. giant tumor, with tilting of the brainstem and deformation of the IV ventricle.

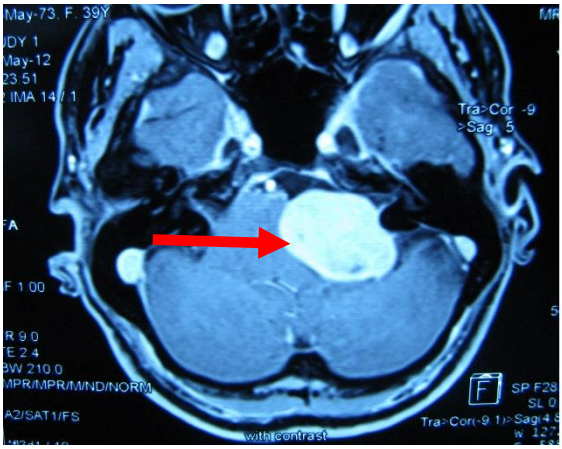

Figure 11. MRI: giant left vestibular schwannoma (acustic neruinoma) (Personal collection of Prof. Dr. AV Ciurea)

The neurinoma can be unilateral or bilateral and predominates in females in the IV-VI decade of life. Classically the evolution comprises several stages: otological, oto-neurological, neurological, HIC and compression of the brainstem.

Semiology of cerebello-pontine angle tumors

There is an anatomoclinical dissociation: the giant tumor shows minimal signs.The clinical pattern consists of the following categories of symptoms:

Otological symptoms:

I.***Auditory:*** unilateral hearing loss that can be progressive in 95% of cases, with brutal installation in 2%, with fluctuating evolution 2%. Audiometry highlights perceptual deafness. In 20% of cases, patients have tinnitus.

II.***Vestibular:*** instability or balance disorders (65%), drunk walking, lateral fall.

Positive signs: Romberg, Barany, Unterberger, Babinski-Weil. Other vestibular signs are vertigo (20%), nystagmus (25%).

III.***Earache:*** feeling of atrial fullness, otic pain, retro-mastoid pain.

Neurological symptoms that reflect the suffering of cranial nerves, cerebellum and brainstem.

Signs of damage to the cranial nerves:

1. Trigeminal nerve: hemiface numbness 30%; neuralgia; corneal reflex diminished or abolished 30%; cutaneous hypoesthesia

2. Facial Nerve: 10%: paresis, hemispasm, hypoesthesia of the external auditory canal, abolition of the nasolacrimal reflex;

3. IX, X, XI Nerves: phonation and / or swallowing disorders, syncope, trapezius muscle atrophy and / or sternocleidomastoid.

Cerebellar damage: in 10% of cases a kinetic syndrome occurs.

Signs of brainstem damage: pyramidal syndrome, bulbar voice, walking in small steps.

Symptoms of HIC: are common and have serious consequences: CSF blockage in the pontocerebellar angle, brainstem tilt, headache, vomiting, intellectual deficit, papillary edema. (5,6,7)

3. Trigeminal schwannoma

It is a rare tumor representing about 2% of cerebello-pontine angle tumors. The tumor can have various locations, depending on the origin, which requires classification into the following 3 types:

- **Type A** is located in the middle fossa, arising from the branches of the Gasser ganglion in the Meckel cavity and may invade the cavernous sinus.
- **Type B** originates from the roots of the nerve or ganglion and develops at the ponto-cerebellar angle.
- **Type C** develops on the rock ridge.

Frequently the first complaint repeated by the patient is hearing loss, secondary to the involvement of the VIII nerve, while neuralgia or facial paresthesia are reported in only a third of cases. Neurological examination reveals facial hypoesthesia and changes in corneal reflex. (7,8)

4. Other schwannomas

Facial nerve schwannoma

It is very rare, the literature mentions less than 200 cases. The tumor can be located on any segment of the nerve: in the pontocerebellar

angle, in the path or through the facial canal that crosses the temporal rock, or on the extracranial trajectory.

Relevant symptoms for facial schwannoma are progressive hemispasm and peripheral facial paralysis. Acoustic-vestibular disorders occur in the context of tumor development in the pontocerebellar angle.

Jugular foramen nerves' schwannomas

Represents 1-1.5% of tumors of the pontocerebellar angle. Less than 200 cases are cited in the literature worldwide.

By location it is classified into four types:

– **type A:** with intracranial localization
– **type B:** with intraosseous localization in the jugular foramen
– **type C:** extracranial, located in the infratemporal spaces
– **type D:** in "bisac", equally intracranial and infra-temporal, crossing the jugular foramen

The symptomatology combines the characteristic signs of the lesions of the pontocerebellar angle with the typical ones of suffering of the nerves IX, X, XI: dysphonia, dysphagia, atrophy of the trapezius or of the sternocleidomastoid muscles.

5. Paraclinical diagnosis of schwannoams

Brain CT examination – plaint, with contrast and bone window is the most commonly used examination to highlight the tumor in the cerebellar-pontine angle, the relationships with the brainstem and cerebellum, tumor extensions and secondary hydrocephalus. The plain CT examination shows an isodense lesion which, when administered with the contrast substance, becomes hyperdense, homogeneous, well delimited, oval in shape, fixed to the rock and centered on the internal auditory canal it occupies. Bone window examination reveals the reshaping of the rock with dilation of the internal auditory canal and the acoustic pore, osteocondensation or osteolysis.

MRI examination is useful for the quality of axial, coronal, and sagittal images and for the detection of small intracanal tumors that are not visible on examination of brain CT.

Cerebral angiography specifies the arterial afferents of the tumor and its vascularization.

Audiometry, auditory evoked potentials and facial electromyography show damage to the cranial nerves in the pontocerebellar angle.

Peculiarities of paraclinical diagnosis

Exclusive EMG examination, which reveals a significant facial denervation, can lead to the diagnosis of a facial lesion and not a vestibulo-cochlear developed in the pontocerebellar angle or the internal auditory canal. (5,10)

Regarding the posterior ruptured hole lesions, the brain CT and MRI examinations show a tumor in the pontocerebellar angle located inferiorly and dilating the jugular foramen, especially in its anterior, nervous part. Coronal and sagittal clichés visualize extracranial tumor extensions in the sac (type D).

Brain CT and brain MRI examinations for trigeminal schwannoma are similar to those for vestibular schwannoma, but the tumor is more internal to the internal auditory canal and dilates the internal acoustic pore. The imaging diagnosis is much more accurate if the tumor appears on the crest of the rock or has a tumor bud extending to the temporal fossa.

6. Treatment principles

The choice of therapeutic means considers the characteristics of the tumor (Antoni A or B, the volume and topography of the lesion), the characteristics of the patient (general condition, age, von Recklinhausen's disease) and the experience of the neurosurgery service.

Surgery can be performed by the neurosurgeon by suboccipital approach (retromastoid craniectomy or craniectomy of posterior hemifossa), ENT by translabyrinthine approach (when deafness has already installed and there is no chance of hearing recovery), and in small tumors below 2.5 cm diameter, can be used for radiosurgery in stereotaxic conditions.

The principles of treatment are the same for both vestibular and trigeminal schwannoma. Complete ablation is the ideal surgical treatment.

Radiosurgery under stereotaxic conditions, either in the focus of convergence of 201 perfectly concentric gamma rays, or through a beam of a radiation source displaced along arcs of a circle centered on the tumor, retains its indications and its value in tumors. small. (11)

The treatment of posterior ruptured hole schwannomas is tumor excision, which is the ideal treatment. In case of subtotal tumor ablation, stereotaxic radiosurgery will be associated.

7. Conclusions

Although they are 100% benign tumors and have a slow growth rate, schwannomas associate a "malignant" character through their deep localizations and relationships with critical neighboring structures. Certain factors have greatly facilitated the surgery of these intracranial tumors in recent decades: the development of imaging techniques that allow a more accurate local characterization of the lesion, improvement of instruments and optical microscopy equipment, the use of monitoring potentials evoked intraoperatively to achieve a wide resection without damage the facial nerve. Stereotactic radiosurgery is a special adjunct for tumor debris or small lesions.

Abbreviations:

IAC – internal auditory canal; **CPA** – cerebello-pontine angle; **CT** – computerized tomography; **MRI** – magnetic resonance imaging; **TCPA** – tumors of cerebello-pontine angle

Disclaimer: The authors have no conflicts of interest to declare.

References:

1. Arseni C., Carp N., Anatomia patologică a tumorilor sistemului nervos, Editura Didactică şi Pedagogică, Bucureşti, 1978.
2. Ciurea A.V., Tratat de Neurochirurgie Vol. 1, Editura Medicală, Bucureşti, 2010.
3. Ciurea A.V., Tratat de Neurochirurgie Vol. 2, Editura Medicală, Bucureşti, 2011.
4. Ciurea A.V., Iencean S., Tumorile intracraniene în Irinel Popescu Tratat de Chirurgie, Vol II - Neurochirurgie, Ed. Academiei Române, Bucureşti, 2007.

5. Ciurea A.V, Iencean S., Mohan D., Simptomatologia tumorilor intracraniene, în Actualități în tumorile intracraniene, Editura Universitară, București, 2011.
6. Constantinovici A., Ciurea A.V., Ghid practic de neurochirurgie, Ed. Medicală, Bucureşti, 1998.
7. Iencean S., Ciurea A.V., Tumori intracraniene în Tratat de Neurochirurgie, Vol. I, Ed. Medicală, București, pg. 388-433, 2010.
8. Kleihues P., Cavanee W., WHO classification of tumours, In Pathology and Genetics: Tumours of the Nervous System, Lyon, France, IARC, 2000.
9. Samii M., Matthies C., Management of 1000 vestibular schwannomas (acoustic neuromas): surgical management and results with emphasis on complications and how to avoid them, Neurosurgery, 40:11-21, discussion 21-13, 1997.
10. Schmidek H.H., Roberts D.W., Operative Neurosurgical Techniques, 5th Edition - Indications, Methods and Results, Saunders, 2006
11. Wu, H., Zhang, L., Han, D., Mao, Y., Yang, J., Wang, Z., Jia, W., Zhong, P., & Jia, H. (2016). Summary and consensus in 7th International Conference on acoustic neuroma: An update for the management of sporadic acoustic neuromas. World journal of otorhinolaryngology - head and neck surgery, 2(4).

POSTERIOR FOSSA TUMORS IN CHILDREN

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Nothing outside of you has power over you
Ralph Waldo Emerson, American essayist (1803-1882)

Contents

1. History

Cushing was the first author to report an extensive series of posterior fossa tumors (PFTs) (61 patients with cerebellar medulloblastoma, most with a poor prognosis) (1).

PFTs are considered critical area lesions, primarily due to the small space of the posterior fossa and the potential for damage to vital nuclei in the brainstem. In cases of acute symptoms of cerebral hernia or damage to the brainstem, emergency surgery may be required.

2. Incidence

PFTs are more common in children than in adults (about 54-70% of all brain tumors in children originate in the posterior fossa, as opposed to 15-20% of all brain tumors in adults). Some histopathological types, such as medulloblastoma (MBL), pineoblastoma, ependymoma, primitive neuroectodermal tumors (PNET), and cerebellar or brainstem astrocytomas, have a higher incidence in children. Other glial tumors, such as mixed gliomas, occur only in children, are frequently located in the cerebellum (67%), and are generally benign.

In a study of 133 PFT in children, the incidence was: MBL 40%, cerebellar astrocytomas 23%, brainstem gliomas 21%, epemdymomas 11%, and a single case of ganglioglioma, haemangioblastoma and teratoma. Extranevraxial tumors accounted for only 3% of cases, including 2 cordomas and 2 schwannomas. Gender predominance was equal for cerebellar astrocytomas, while MBL, brainstem gliomas, and ependymomas were more common in males. Most astrocytomas were midline, probably originating in vermis. The incidence of calcifications on CT scan was higher in ependymomas (69%), MBL (29%), cerebellar astrocytomas (17%), and brainstem gliomas (8%) (2).

PFT represents 2/3 of all tumors in pediatric age. Most of them are MBL, pilocytic astrocytomas and ependymomas, which together account for about 90% of cases. Astrocytoma (in 97% pilocytic cases) is the most common PFT in children (3)(4). After surgical resection, the 5-year survival rate is over 90% (5)(6).

MBL is a tumor specific to the posterior fossa, more common in children under the age of 7 years, with an incidence in children of about 50% (4)(6). Treatment and prognosis vary with age and tumor size as well as the location and degree of invasion, with a survival rate of 70% (3) at 5 years, but the prognosis is more unfavorable in children aged 2-3 years. Surgical resection is mandatory in the treatment of these tumors, but in children older than 4 years, radiotherapy can prevent dissemination, especially after incomplete surgical resections or relapses. Chemotherapy combined with radiotherapy improves the survival rate by up to 60%.

3. Etiology

To date, no specific causes for PFT have been found. Sometimes, genetic factors such as dysfunction in certain tumor suppressor genes (p53 gene) and activation of oncogenes may play a role in the development of these tumors (6). Even certain environmental factors such as irradiation or toxins may play a role in this.

Some tumor-specific methylated genes, such as COL1A2, S100A10, S100A6, HTATIP2, CDH1, LXN, show increased methylation levels compared to the normal cerebellum. Recent studies show that COL1A2 plays an important role in MBL tumorigenesis. Dense biallelic methylation associated with lack of transcription was observed in 77% of cases. In addition, the COL1A2 status distinguishes between the infant's MBL and the desmoplastic histopathological subtype, indicating a distinct molecular pathogenesis of this tumor type that gives him a more favorable prognosis (4). Other alterations found in MBL are: the presence of p53 and HER2 oncoproteins, increased mitotic index and the presence of neuronal differentiation. A recent study determining the immunohistochemical expressiveness of the markers Ki-67, NeuN, synaptophysin, HER2 and p53 in 40 MBL samples and their correlation with clinical parameters and survival rate, shows that in 72.5% of cases, more than 20% of the cells were positive for Ki-67. Males have a higher Ki-67 expressiveness and a lower survival rate. NeuN and synaptophysin were negative in 40% and 20% of cases, respectively. P53 was positive in 45% of cases. HER2 was positive in 57.5% of cases and did not show a statistically significant association with the

survival rate. Other studies show that resveratrol (3,5,4'-trihydroxy-trans-stilbene) induced neuronal differentiation in MBL cells (8).

4. Classification

PFTs can be located on the midline or laterally in the cerebellar hemispheres, pontocerebellar as well as brainstem.

The most common TFPs are the following:

1. Cerebellar astrocytoma. Cystic cerebellar astrocytoma accounts for about **33%** of all PFT in children and 25% of all tumors in pediatric age. The average age at presentation is 9 years. This tumor may be located laterally in the cerebellar or medial, in the vermis, with a well-defined cyst and solid component. The posterior fossa pilomixoid astrocytoma has recently been described in the literature (9).

2. Primitive neuroectodermal tumors (PNETs) include MBL, medullary epithelium, pigmented MBL, ependimoblastoma, pineoblastoma, and cerebral neuroblastoma. They originate in undifferentiated cells in the subependymal region of the fetal brain. PNET represents **25**% of intracranial tumors in children, being on the 2nd place as incidence after cerebellar astrocytoma.

3. Medulloblastoma (MBL). MBL originally originates in the lower medullary veil and increases by filling the IV ventricle and infiltrating neighboring structures. Newer classifications include them in the PNET category. MBL extends by contiguity to the cerebellar peduncle, the floor of the IV ventricle, the cervical or supratentorial spinal cord. This tumor also spreads through the intracranial or spinal CSF, therefore patients should be neuroimaging (preferably by MRI) throughout the nevrax and, if possible, CSF analysis should be performed for tumor cells (10)(11). Sometimes MBL **can metastasize outside the CNS, especially in the bones.** Patients with disseminated lesions have an increased risk of recurrence (12). **Other unfavorable prognostic factors are young age, brainstem damage, subtotal resection and histopathological aspects of anaplasia** (2)(41)(66)(93). Also, the nuclear expressiveness of p53 and the interruption of the p53 / ARF tumor suppressor pathway, the expressiveness of HER2 / ErbB2 and survivin (16-18) as well as the amplification and hyperexpressivity of MYCC / MYCN have been shown to be unfavorable prognostic factors

in some studies (19-22) but not in all cases (17). Two major groups of risk categories based on clinical criteria have been described in the literature: Medium risk: Children older than 3 years, with PFT in which the tumor was totally or almost completely resected (residual tumor <1.5 cc) and without dissemination (15). Increased risk: Children 3 years of age and older, metastatic tumor or subtotal resection (residual tumor> 1.5 cc) and / or location other than the posterior fossa (22).

4. Ependymoma and ependimoblastoma. Ependymoma is a tumor originating in ependymal cells. It is predominant in females and in 50% of cases occurs in children under 3 years. Ependymoma has a better prognosis than ependimoblastoma, it fills the ventricular space without adhering to the ventricles.

5. Choroid plexus papilloma (CPP) and **choroid plexus carcinomas (CPC)**. These tumors represent 0.4-0.6% of all intracranial tumors. They are more common in children than in adults, accounting for 3% of brain tumors in children. *It is located 60% in the lateral ventricles and 30% in the IVth ventricle. IIIrd ventricle and pontocerebellar angle are rare locations.* **They cause a hypersecretion of CSF that can exceed 4 times the normal volume** and fluid analysis reveals **hyperproteinemia and / or xanthochromia**.

6. Dermoid tumors. These tumors are due to the incomplete separation of the epithelial ectoderm from the neuroectoderm at the level of the anterior neuropore in the 4th week of gestation. It is **a cystic tumor that contains hair follicles, sebaceous glands and fat**. The tumor grows slowly, through epithelial exhumation and progressive accumulation of sebum and rupture of the cyst causes aseptic meningitis. They are frequently located in the posterior fossa or midline and may be extradural, vermicular or intraventricular.

7. Neuroblastoma, ganglioneuroblastoma (GNB), and ganglioneurinoma are tumors with varying degrees of histological maturation, derived from primordial neural crest cells that form the **sympathetic nervous system**. The presence of immature cells in neuroblastoma and GNB represents a potential for malignancy. These tumors are located anywhere in the sympathetic nervous system such as the neck, posterior mediastinum, adrenal glands, retroperitoneum and pelvis (23)(24). CNS localization is extremely rare and most cases

occur under the age of 2 years, although it can also occur in older children or young adults. It is generally located in the cerebral hemispheres (23)(25), but can also occur in the pineal gland (81) or spinal cord (27). Cerebellar GNB is extremely rare, only one such case has been published in the literature (28).

8. **Hemangioblastoma**. Hemangioblastoma accounts for 7-12% of total PFT and about 70% of those located in the cerebellum are **cystic**. It has a predominance for males and the average age at presentation is 30-40 years. Hemangioblastoma **may be associated with von Hippel-Lindau** disease.

9. **Meningioma.** Rare in children.

10. **Schwannoma**. It rarely occurs in children, usually in the context of a **Recklinghausen's disease**, a situation in which it is often bilateral.

11. **Brainstem tumors**. These represent 15% of all brain tumors. In children, brainstem gliomas represent 25-30% of all brain tumors, most of which are small-grade astrocytomas.

5. Clinical symptoms

The clinical symptomatology depends on several factors such as: tumor location, histopathological appearance and lesion aggressiveness, as well as the rate of tumor recurrence.

- On admission, patients suffer the most from headaches and vomiting associated with hydrocephalus (HY).
- Focal symptoms due to compression of the cerebellum or centers in the brainstem, which also causes increased intracranial hypertension (ICH) (10).
  - Symptoms due to compression of the brainstem are manifested mainly by dysfunctions of the cranial nerves, the most commonly affected being the nerves or nerve nuclei **III, IV and VI** leading to paralysis or diplopia. Signs of compression of the long tracts are manifested by **hemiparesis**.
  - Symptoms due to focal compression of the cerebellum include characteristic ocular symptoms and vermian syndrome. Trunk ataxia (tendency to fall and walking with a broad support base) is a common manifestation in midline tumors such as MBL, vermis astrocytomas or ependymomas. **Hemicerebellar syndrome** includes: ataxia of the

contralateral limbs of the affected cerebellar hemisphere, nystagmus and asymmetry. These tumors can be metastases, cerebellar astrocytomas, or hemangioblastomas. **Nystagmus** is generally manifested in the advanced stages of the disease and can be of 2 types: **vertical** - in lesions of the anterior vermis, periapeductal region or craniocervical junction and **horizontal** - in diseases of the cerebellar hemisphere.

- Intracranial hypertension (ICH) causes the following symptoms:
  - **Headache**: This is the most common symptom in PFT. If the headache is associated with neck pain, neck stiffness, or torticollis, it may suggest a syndrome of cerebellar amygdala involvement in the foramen magnum. TFP headache is intermittent, more severe in the morning or during sleep, due to increased PIC. In children, it may be accompanied by irritability.
  - **Vomiting**: These are caused by either HIC or irritation of the vagal nuclei in the brainstem or the posterior area of the IV ventricle. Jet vomiting, not preceded by nausea, usually occurs in the morning.
  - **Strabismus**: Due to paresis of the VIth nerve. Sometimes paresis of IIIrd nerve can occur.
  - **Visual disturbances** due to papillary edema
  - **Meningism**
  - **Vertigo**
  - **Macrocephaly**
  - **Hydrocephalus**

6. Laboratory studies

Tumor markers

- a carcinoembryonic antigen (ACE)
- an alpha-fetoprotein (AFP)
- placental proteins.

7. Neuroimagistic studies

1. **Simple X-ray of the skull**

- May show signs of chronic HIC.

- Calcifications
- Bone defect with sclerotic edges in dermoid cysts

2. **CT scan** (computed tomography): CT scan is less useful than MRI in diagnosing PFF but is very useful in postoperative follow-up.

3. **Angiography**

- Shows the vascularization of the tumor and the origin of the nutrient vessels
- In TFP angioRMN is preferred

4. **Nuclear magnetic resonance (MRI)** - general data

MRI in cerebellar astrocytoma

- Expansive process of midline or cerebellar hemisphere (Fig 1)
- Obvious **cystic component**, hypointense in T1 sequences and slightly hyperintense in T2 sequences due to high protein content
- The most obvious wall node in T2 sequences
- Moves or fills the IV th ventricular cavity
- Obstructive hydrocephalus (Fig. 2)
- The node that is loaded with paramagnetic contrast agent
- Cystic wall with or without contrast socket
- Rare heterogeneous appearance or calcifications

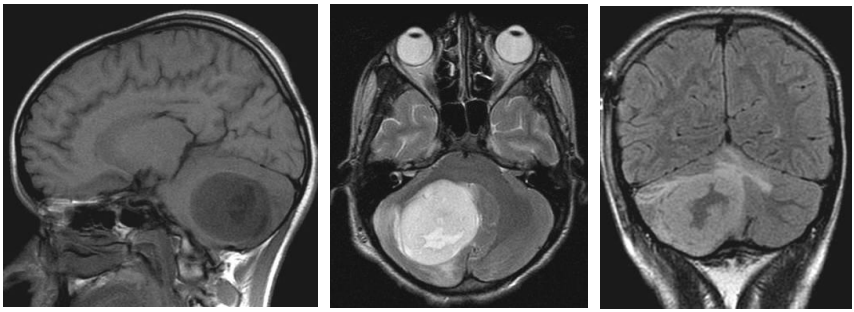

Figure 1. Right cerebellar hemisphere pilocytic astrocytoma – T1 and T2 MRI.
(Personal collection of Prof. Dr. AV Ciurea)

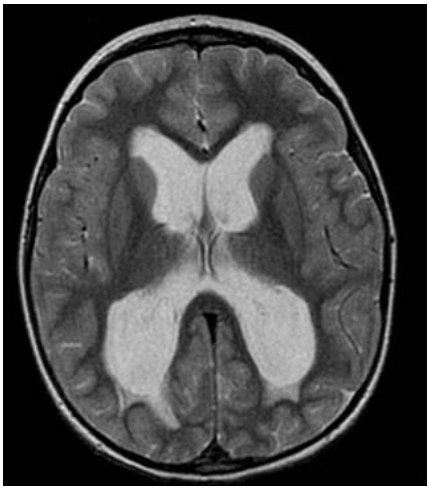

Figure 2. Obstructive hydrocephalus – T2 sequence MRI.
(Personal collection of Prof. Dr. AV Ciurea)

MRI in PNET

- Expansive process of intraventricular or paramedian midline, isointens in T1 sequences
- Loads intensely with contrast medium
- Sometimes heterogeneous appearance with cystic areas and central necrosis
- Sometimes calcifications, eccentric localization or absence of contrast

MRI in ependymomas (Fig. 3)

- Frequently located intraventricularly
- Plastic ependymomas extend through Magendie and Luschka holes compressing craniocervical junction and brainstem
- **Extension to the pontocerebellar angle** is pathognomonic for ependymomas
- Contrast shot, often heterogeneous
- Calcifications in 45% of cases

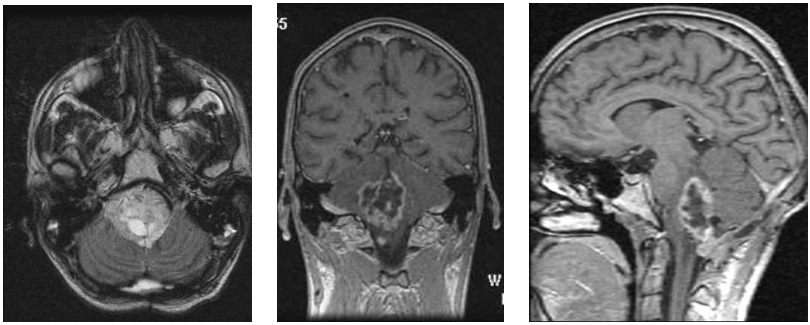

Figure 3. IVth ventricle ependimoma. T1 sequence in contrast MRI. (Personal collection of Prof. Dr. AV Ciurea)

MRI in hemangioblastoma

- Cystic mass plus wall node with pial insertion, slightly hyperintense and with marked contrast socket (Fig 4)
- Abnormal vessels can be found adjacent to or inside the tumor
- The cystic content can be isointense or hyperintense in T1 and T2 sequences
- The cystic wall is well delimited
- Sometimes intracystic hemorrhages may occur, predominance of the solid component compared to the cystic one, multiple lesions or syringomyelic cavity

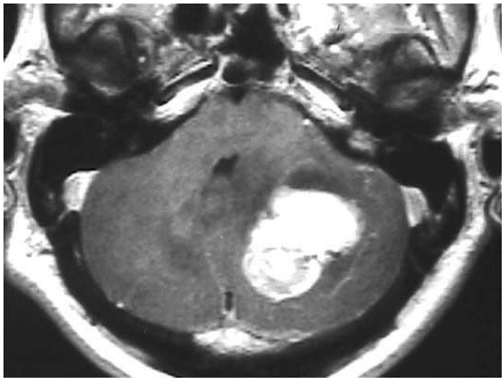

Figure 4. Left cerebellar hemangioblastoma. T2 sequence in contrast MRI. (Personal collection of Prof. Dr. AV Ciurea)

MRI in choroid plexus papilloma (CPP) (Fig. 5)

- Intraventricular mass with lobed edges, hypointense in T1 sequences
- Calcifications and hypervascularization, hyperintense in T2 sequences
- Marked contrast socket
- Extension through Luschka or Magendie holes to basal tanks (80)
- Hydrocephalus

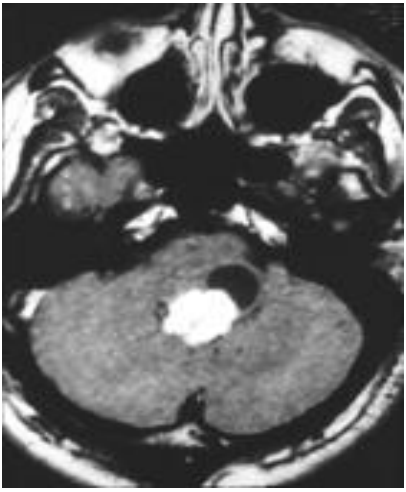

Figure 5. IVth ventricle choroid plexus papilloma.
T1 sequence in contrast MRI.
(Personal collection of Prof. Dr. AV Ciurea)

MRI in dermoid cyst (Fig. 6)

- Hyperintense images in T1 sequences and hypointense in T2 sequences
- Located on the midline

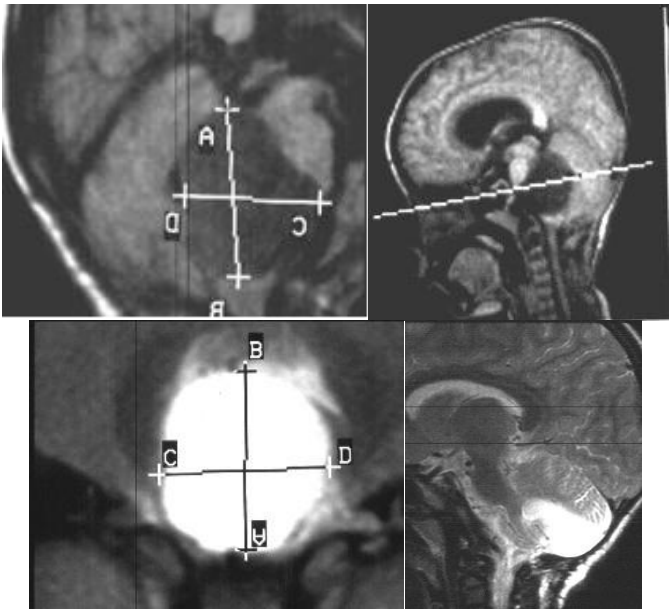

Figure 6. Posterior fossa dermoid cyst. MRI T1 and T2 sequences.
(Personal collection of Prof. Dr. AV Ciurea)

MRI in meningiomas (Fig. 7)

- MRI in posterior fossa meningiomas reveals a hypo- or hyperintense tumor mass, with a homogeneous, well-defined contrast, without significant perilesional edema.

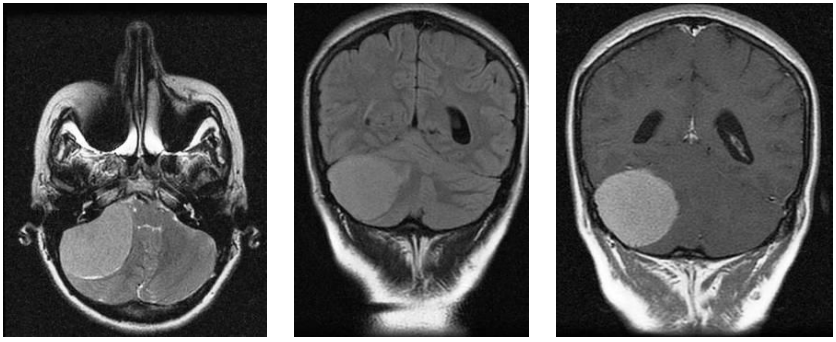

Figure 7. Posterior fossa meningioma. MRI T1 sequences.
(Personal collection of Prof. Dr. AV Ciurea)

8. Histologic findings

1. Cerebellar astrocitoma

- Pilocytic astrocytoma represents about 61% of posterior fossa astrocytomas. Most astrocytes are fibrillar, with round-oval nuclei, cytoplasmic pleomorphism and Rosenthal fibers. It has denser cellular areas, which alternate with absent cellular areas. (Fig. 8)

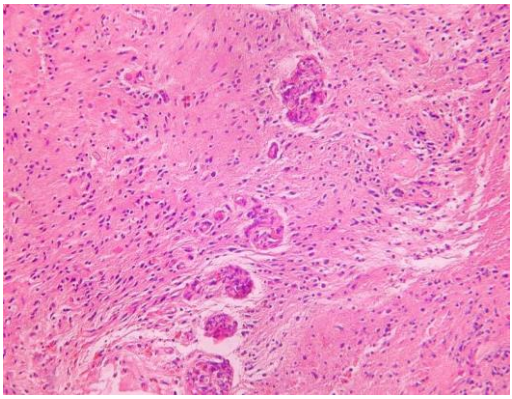

Figure 8. Pilocytic astrocytoma

- Fibrillar infiltrative astrocytoma represents about 28% of posterior fossa astrocytomas. This type occurs more frequently in adults. This type has histopathological aspects of anaplasia. (Fig. 9)

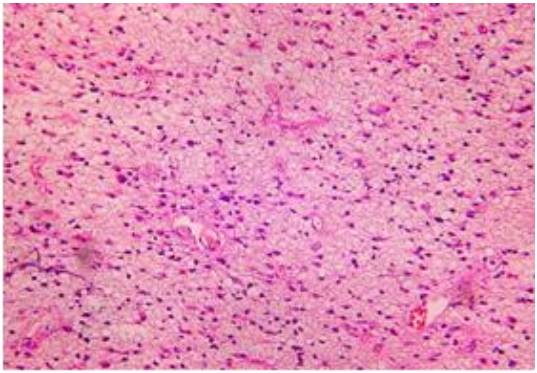

Figure 9. Fibrillar astrocytoma

- Anaplastic astrocytoma represents about 11% of posterior fossa astrocytomas. Anaplastic aspects are more common. (Fig. 10)

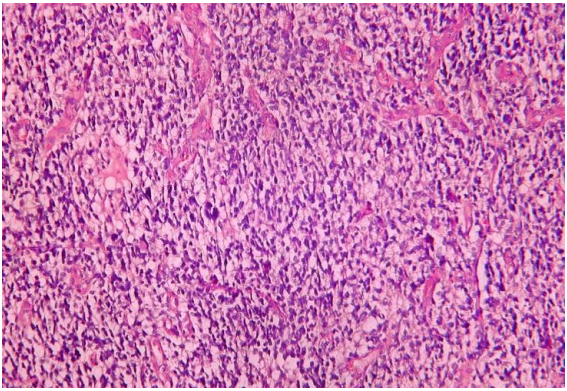

Figure 10. Anaplastic astrocytoma

2. Meduloblastoma

- Macroscopically it appears as a soft and friable tumor mass, often with areas of necrosis and focal hemorrhage.
- Calcifications are rare.
- The tumor infiltrates the brainstem and cerebellum in about 30% of cases.
- Dissemination along the subarachnoid space is common, with metastatic lesions being present in 50% of autopsied cases.
- Hypercellularity, with round-oval cells and hyperchromic nuclei. (Fig. 11)
- Homer-Wright rosettes and pseudo-rosettes are common, suggesting neuronal differentiation.

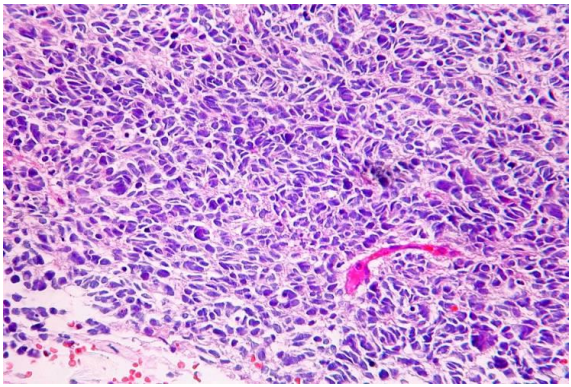

Figure 11. Meduloblastoma

3. Ependimoma

- Uniform-looking cells, grouped around the vessels, forming perivascular pseudoroses.
- Typical ependymal rosettes.
- Cells contain blepharoplast.

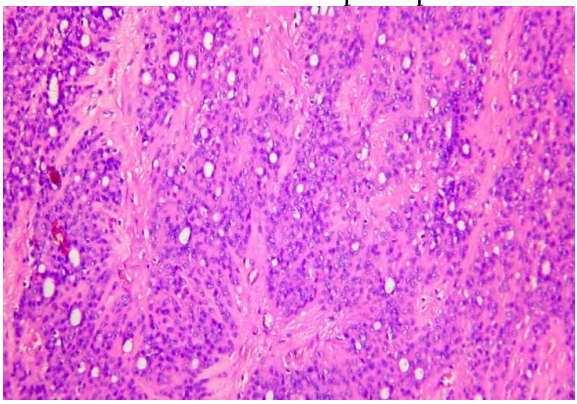

Figure 12. Ependimoma

4. Ependimoblastoma

- Nuclear and cytoplasmic pleomorphism
- Hyperchromic nuclei.
- Excessive mitosis.

- Necrosis
- Disorganized cytoarchitecture

5. Choroid plexus papilloma (CPP)

- Macroscopically it appears as a reddish mass with an irregular surface.
- Microscopically shows cuboidal epithelial cells similar to those of the normal choroid plexus. (Fig. 13)

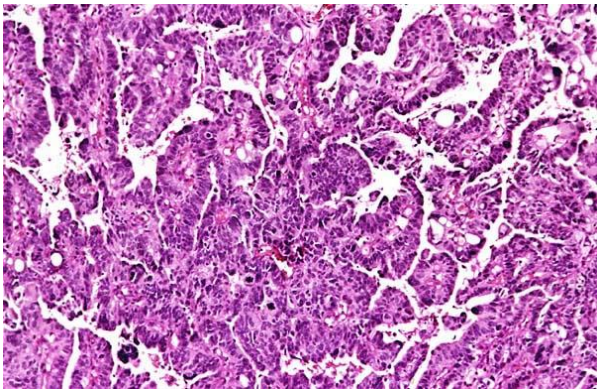

Figure 13. Choroid plexus papilloma

6. Hemangioblastoma

- Macroscopically it appears as a dark yellow tumor. The wall nodule is in contact with the pial surface of the cerebellum and in 20% of cases, the dura mater is affected by the lesion. The cystic wall and its contents have a white-yellow appearance.
- Microscopically it appears as a benign cell proliferation with vascular canal formation and the stromal reticulin network and fat-laden cells are characteristic features.

9. Medical tratament

Prior to surgery, diuretics or corticosteroids may be given to reduce edema in structures adjacent to the lesion.

10. Preoperative considerations

A thorough assessment of the patient's general condition should be performed. Tumor side effects, such as HIC, should be treated with specific, depletive medication and dexamethasone - 1 mg / kg / day.

Symptomatic obstructive HY can be treated before tumor resection by shunt or external ventricular drainage. Newer studies have tried to find a correlation between ventricular volume (measured MRI) in HY, which indicates ventricular drainage, tumor size, and the relationship between these components in children with MBL. According to these authors, the mean preoperative ventricular volume was 252 ml in patients who required drainage and 106 ml in those who did not require preoperative drainage. A statistically significant correlation was found between preoperative ventricular volume and tumor volume in patients requiring drainage. MBL resection has also been found to transform obstructive HY into a communicating one that requires surgical treatment if it exceeds a certain level of CSF volume (29).

Neurological damage may require emergency surgery for tumor resection. TFP surgery has the following objectives:

- **Decompression of the posterior fossa** to reduce the pressure exerted by the lesion on the brainstem and decrease the HIC that could cause cerebral hernias.
- **Histopathological diagnosis** of the lesion
- Determining a correct **postoperative management plan**, including adjuvant therapy where appropriate
- HY treatment by shunt or external ventricular drainage when appropriate (30)

11. Intraoperative considerations

- **Patient positioning**
  - The "prone" position is more comfortable for the surgeon.
  - The sitting position presents the risk of pulmonary embolism and is less comfortable for the surgeon but the operating field is clearer due to gravitational drainage. Some authors consider

that the postoperative evolution of patients operated in this position is better (63)

- **Safety drill hole**:
  - It is placed in the occipital area and can be used in case of acute HY that requires ventricular drainage.
- **Surgical approaches**: The most common approaches used in PFT are
  - On the midline
  - Paramedian
  - Retromastoid
  - Telovelar
- **General principles**
  - The incision on the midline extends from the inion to the first cervical vertebra (Fig 14)
  - Craniectomy depends on the location and size of the tumor. (Fig. 15)
  - The foramen magnum opens, and the arch of the C1 vertebra can be removed, especially in tumors extending to the craniocervical junction.
  - Dura mater is incised in a Y-shape with the base upwards.
  - Tumor resection is done by light suction with the ultrasonic aspirator or, less often, with the CO_2 laser.
  - Extension of tumor resection should be performed so as to minimize the risks of complications, especially in tumors adhering to the brainstem.
  - Dura mater closes tightly, and if necessary, a dural graft can be used.
- **Special considerations**
  - CPP should be completely resected as benign tumors that do not invade the brain.
  - In dermoid cysts with dermal sinuses, the sinus must be removed completely.

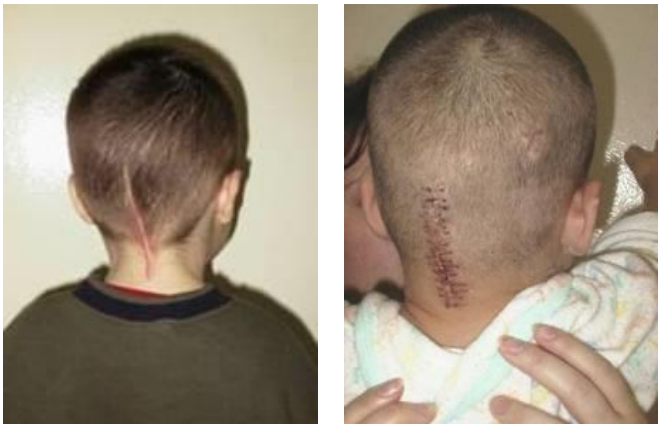

Figure 14. Median incision extended from the inion to cervical column.
(Personal collection of Prof. Dr. AV Ciurea)

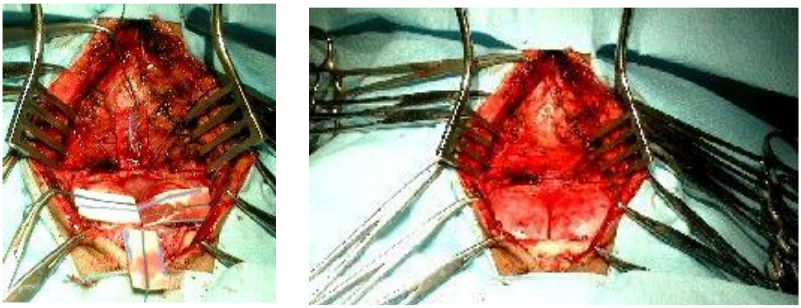

Figure 15. Posterior fossa median craniectomy.
(Personal collection of Prof. Dr. AV Ciurea)

12. Complications

Possible complications in PFT surgery are: inferior cranial nerve dysfunction or facial paresis, deficits caused by long tract damage, hemiparesis or hemiplegia, sensitivity disorders, infections, prolonged coma, obstruction or shunt dysfunction, pulmonary infections, deep vein thrombosis pulmonary, CSF fistula.

13. Meduloblastoma (MBL)

Collins' law stated that a child with MBL is considered cured after a period that includes the child's age at the time of diagnosis plus 9 months (31). Recent studies show that this law is frequently violated and consider that this concept should be abandoned in the MBL (32). Complete postoperative evaluation of an MBL is the essential key to correct treatment. The main objective of the surgical procedure must be the maximum possible resection of the tumor. Children with disseminated MBL at the time of diagnosis show an improvement in the rate of tumor survival and progression if the postoperative tumor residue is minimal (33). MBL surgery can sometimes be associated with temporary or permanent neurological worsening due to postoperative infections, direct cerebellar injury, or the development of postoperative mutism syndrome. This syndrome, with late onset, usually a few hours postoperatively, is characterized by mutism, emotional lability, hypotonia, dysphagia, and ataxia and has been reported in about 25% of cases. The etiology of mutism in TFP surgery is still unclear, but has often been attributed to tumor invasion of the brainstem, vermis lesions, and possible disruption of the dentatotalamocortical pathways. This incident causes permanent sequelae in about 50% of moderately or severely affected patients (34). Postoperative evaluation should be aimed at determining the patient's increased risk of recurrence. Risk criteria are defined in the staging of the disease (35)(36). Patients with metastases or significant residual tumors are considered high-risk patients.

MBL grading

MBL staging depends on the extent of resection, radiological evidence of tumor dissemination and CSF cytology. The TNM staging system proposed by Chang (38) has more recently been simplified into high or low risk categories. Patients undergoing total resection without radiological evidence of malignancies and without tumor cells on CSF cytological examination are considered low-risk patients (low risk: T1, T2, T3a, M0 and lack of residual postoperative tumor). Increased risk includes patients with T3b, T4, and any M + or the presence of residual postoperative tumor.

Chang Scale:

Tumor stage (T)

- T1: tumor less than 3 cm in diameter that affects one of the structures of the posterior fossa
- T2: tumor less than 3 cm in diameter that invades two or more structures of the posterior fossa
- T3a: tumor larger than 3 cm in diameter that invades two or more structures of the posterior fossa
- T3b: tumor that invades the floor of the IV ventricle
- T4: tumor extending outside the IV ventricle, superior to the III ventricle, caudal to the magna cisterna or associated with severe HZ.

Metastasis stage (M)

- M0: no tumor spread
- M1: positive lumbar CSF cytology
- M2: intracranial dissemination of the tumor
- M3: spinal spread of the tumor
- M4: systemic dissemination

Therapeutic options depending on clinical status

The Children's Oncology Group (COG) coordinated a randomized experimental phase III in children aged 3-8 years who received craniospinal irradiation with 18-24 Gy, as well as patients aged 3-21 years who underwent conformal irradiation on the tumor locus, respectively irradiation of the posterior fossa. In this study, children received weekly vincristine during irradiation therapy and lomustine, vincristine, cisplatin, etoposide, and cyclophosphamide after radiation therapy. Two risk groups were classified: (36)

- Medium risk: The classic postoperative treatment of patients in this group consists of radiotherapy at doses of 54-55.8 Gy on the posterior fossa and about 36 Gy on the entire nevrax. Some studies show that in MBL irradiation on the posterior fossa can be replaced by irradiation located strictly on the tumor bed, with the same efficiency (33) and lower toxicity (39)(40). However, to date, the minimum irradiation dose required to control the disease has not yet been established. Attempts to reduce the dose of craniospinal radiotherapy

to 23.4 Gy without the administration of chemotherapy have increased the incidence of isolated leptomeningeal recurrences (87). Decreasing the irradiation dose on nevrax to 23.4 Gy, associated with chemotherapy, shows a control of tumor growth in 80% of cases and a reduction in neurocognitive sequelae (42-45).

- Increased risk: In patients at high risk, adjuvant chemotherapy increases survival time (35)(42)(46)(47) so that 50-65% of patients have a long-term survival (35). Patients included in this category have extensive and unresectable local tumor and / or metastatic tumor inside or outside the CNS.

A group of 77 children with standard and elevated neuroectodermal MBL were treated with sandwich chemotherapy. The first group was treated with high doses of chemotherapy supplemented with bone marrow autotransplantation and peripheral stem cells. The results show that the 7-year non-recurrence survival rate was 0.66 +/- 0.05 while the sandwich chemotherapy administered to the standard risk group was 0.84 +/- 0.08 at 7 years. The authors conclude that high-dose chemotherapy combined with bone marrow and peripheral stem cell autotransplantation results in a 6-year non-recurrence survival rate of 0.77 +/- 0.08 in patients with high-dose chemotherapy and only 0.46 +/- 0.10 in those without high doses of chemotherapy (48).

Children under 3 years of age with MBL

Because extensive radiotherapy, especially craniospinal irradiation in children under 3 years of age with MBL, causes severe neurocognitive deficits, the possibility of treating them with chemotherapy has been studied (36)(49)(50). Various combinations of chemotherapeutics have been used, most of them using an alkylating substance (cyclophosphamide or ifosfamide), cisplatin and / or carboplatin, oral or intravenous etoposide, and vincristine. The prognosis of these treatments was relatively unsatisfactory, providing a tumor control rate in only 20-30% of patients. Most children who had long-term benefits were those with undisclosed tumors and completely resected. New substances or multi-agent therapy, including intravenous or intraventricular methotrexate, have been sought to increase the efficacy of chemotherapy (51). Thus, in patients with completely resected and

non-disseminated tumors, the 5-year survival rate without tumor progression increased to 60% after the addition of methotrexate. Similar results were obtained in children undergoing high doses of chemotherapeutics with additional peripheral stem cell therapy support (52). However, methotrexate has increased neurotoxicity when administered in high or intraventricular doses, leading to an increased rate of leukoencephalopathy (51). In children with localized MBL and aged 3 years or less, combined chemotherapy followed by radiation therapy may be applied to the tumor bed.

In MBL, radiation therapy is performed at both the cerebral and spinal levels. Adjuvant chemotherapy in high-risk patients is based on the formula cyclophosphamide-cisplatin-vincristine (53).

Recurrent MBL in children

Recurrences in MBL are common and occur a few years after initial treatment (47). Recurrences may be local or distant due to CSF dissemination: in spinal and intracranial leptomeninges, alone or in combination. About 60% of patients with localized MBL will have dissemination at the time of recurrence, even after doses of craniospinal irradiation of 36 Gy (54). Dissemination outside of nevrax is extremely rare (1-2% of recurrences), and has been reported especially in patients treated with radiotherapy alone (54). In recurrences, a complete assessment of the extent of recurrence is required and biopsy or surgical resection is required for histopathological confirmation because other tumors that may occur after radiation therapy and irradiated necrosis are difficult to differentiate from a tumor recurrence. Recurrent MBLs are treated with chemotherapy and / or stereotactic radiotherapy (1) although long-term disease control is relatively rare (55-57). In these patients, new therapeutic models such as high-dose chemotherapy and autologous stem cell therapy may be applied, especially in relapses following single radiotherapy or radiotherapy plus chemotherapy (23)(37)(39).

14. Pilocytic astrocytoma (PA)

Cerebellar astrocytomas represent the majority of benign tumors of the CNS. 70-80% of these occur in children. A study performed on 38

children with posterior pitous cerebellar astrocytomas reveals that they are more prevalent for females (25/38; 66%) than for males (13/38; 34%). The histopathological distribution was: pilocytic astrocytomas 71%, diffuse fibrillar astrocytomas 21%, anaplastic astrocytomas 2% and glioblastomas 6%. The most common location was in the right cerebellar hemisphere and the most common clinical symptom was HIC. All patients were treated surgically, with total resection obtained in 83% of cases and subtotal in 17%. The ventriculo-peritoneal shunt for HY was required in 16% of cases after tumor resection. The most common complication was ataxia and the mortality rate was 8.5% (58).

AP is the most common form of glioma in children. It has a slow growth. Sometimes PA is associated with neurofibromatosis type 1, a situation in which genetic studies identify the pattern of expressiveness of a single gene. AP is a well-circumscribed tumor that grows slowly, is often cystic, and occurs frequently in children. A recent study conducted on 120 PAs in children reveals a male prevalence of 68.3%, and a preferred location in the posterior fossa 61.7%. The histopathological pattern was biphasic in 89.2% with Rosenthal fibers in 66.7% of cases and eosinophilic granular corpuscles in 60% of cases. Vascular aspects were characterized by perivascular hyalinization in 51.7% of cases, angiomatous proliferation in 21.7% and glomeruloid changes in 21.7%. Haosiderin-laden macrophages were found in 37.1% of cases, and 60.8% had lymphocytoplasmic infiltration, while atypia and necrosis were present in 25.8% and 1.7% of cases, respectively. Angiomatous proliferation and hemosiderin deposition were statistically significantly correlated with age 12 years or less (59). Some authors consider that histopathological quantification of tumor vascularization is a prognostic factor in adult astrocytomas but not in children. Thus, the application of antiangiogenetic agents is not valid in children's astrocytomas, especially in AP (7).

Tenascin-C (TN-C) is a brain glycoprotein of the extracellular matrix that in vitro and in vivo studies have shown to have a role in stopping the aggressiveness of astrocytomas, especially in their invasion tendency, but the results are controversial in present. A recent study looked at the action of this substance in 54 PAs (WHO grade I) and 53 diffuse fibrillar astrocytomas (WHO grade II). Studies show that while

TN-C is well expressed in supratentorial white matter, it is absent in infratentorial white matter. In the case of tumors, too, the expressiveness of TN-C differs depending on the location of the tumor. TN-C is an independent prognostic factor when elevated in grade II astrocytomas, in which increased expressiveness correlates with an increased risk of recurrence (60).

AP is a benign tumor that can very rarely spread along the nevrax (only 5 such cases were published by 2003). Several patterns of presentation or recurrence of these tumors have been described, such as: local recurrence, malignant transformation, multicenter disease and metastases. Leptomeningeal dissemination and multicenter disease are distinct pathological entities. HY, biopsy and partial resection are favorable factors for DL (61). A study performed on 4 children aged 2.5-8 years with DL from PA reveals that treatment with high doses of cyclophosphamide has a certain clinical benefit. Of these 4 children with posterior fossa AP, 3 were initially treated surgically and one of the 3 was given radiation therapy. DL occurred at 32, 44, and 8 months of diagnosis, respectively. In the 4th patient with optical pathway tumor, DL was already present at the time of diagnosis. When cyclophosphamide therapy was initiated, DL was present in the subarachnoid space (intracranial 2; spinal 4), in the cerebral ventricles (2), and locally (3). The CSF test was negative in all cases. Cyclophosphamide treatment 4-5 g / m2 / cycle was administered at 4 weeks for 2 cycles in 1 case and 4 cycles in 3 cases. In 1 patient, the disease was stabilized during the 27-month follow-up period, and in 3 patients, a significant reduction in tumor size was observed. Subsequent intrathecal therapy was administered to 2 patients. In 2 patients, the disease progressed 10 and 9 months, respectively, after stopping chemotherapy. One of the re-treated patients responded to a low dose of cyclophosphamide subsequently administered (62).

Other studies have looked at the effect of gamma knife (GK) radiosurgery on AP. Thus, 19 patients, of which 16 children were treated with GK on small residual tumors postoperatively. Most tumors were treated with a prescription dose of 10-12 Gy (between 9-20 Gy). The maximum dose was 22-30 Gy (between 10-50 Gy). The average clinical follow-up period was between 7-8.5 years, and the radiological period

was 4.7-5.9 years. Tumor control was achieved in all cases, and in 85% of cases there was a reduction in tumor volume after GK despite the low prescription dose administered. Post-radiotherapy adverse events were reported in 25% of cases within the first 7 months but resolved later (63).

The long-term prognosis for incompletely resected benign cerebellar astrocytomas in children is unpredictable, with the incidence of symptomatic recurrences ranging from 18-100%. For this purpose, a study was performed on 31 children with such incompletely resected conditions, followed for a long time, none of them showing no type 1 neurofibromatosis (NF1). The histopathological pattern included 22 classical PAs and 9 diffuse astrocytomas. Of the total cases, 17 children showed symptomatic recurrences at 25-450 months, and 14 remained in good condition for 84-516 months. From a neuroimaging point of view, it was not possible to differentiate factors that would explain the difference in evolution between the two groups. In 7 cases CT and MRI were negative. In 2 cases, growth arrest or regression of the rest of the tumor was noted. Data from the literature reveal that radiologically, stopping tumor growth or spontaneous regression of benign cerebellar astrocytomas was 32.5% and 14% of cases, respectively. In conclusion, a large proportion of benign cerebellar astrocytomas do not progress or even regress after incomplete surgical resection. For this reason, if the tumor residue is too risky to be surgically resected over time, careful clinical and radiological follow-up of patients is preferable (64).

15. Ependimoma

In ependymomas, craniospinal irradiation should be considered because the potential for subarachnoid dissemination has been highlighted, especially in the anaplastic type and in those located at the level of the IV ventricle. Recurrence cases are treated by adjuvant chemotherapy with BCNU and dibromodulcitol (65).

16. Choroid plexus papyloma (CPP) and choroid plexus carcinoma (CPC)

Choroid plexus tumors are rare and of neuroectodermal origin, they represent less than 1% of intracranial tumors at all ages. Most cases occur in children under 2 years of age (38). PPC represents over 3% of

intracranial tumors in children, 4-6% of intracranial tumors in children under 2 years of age and 12-13% of intracranial tumors in children under 1 year of age. PPC is associated with Hippel Lindau syndrome and the gender distribution is 2.8: 1 between males and females. PPC may also be associated with Li-Fraumeni syndrome (autosomal dominant syndrome characterized by mutation of the TP53 gene) as well as with Aicardi syndrome (66).

PPCs originate in the isolated layer of cuboidal epithelial cells that cover the papillae of the choroid plexus. They are more common in the trigone and lower horn of the lateral ventricles, in the Monro hole and the ceiling of the third ventricle, and in the posterior fossa they originate in the floor of the fourth ventricle.

Numerous chromosomal abnormalities have been found in choroid plexus tumors, but they do not significantly affect survival. However, some studies have found a higher survival rate in patients with choroid plexus carcinomas and chromosomal abnormalities + 9p and -10q (67).

The treatment of choice in choroid plexus tumors is surgical and lately, minimally invasive endoscopic approaches have become widespread in this type of lesion. Some authors report complete resection of intraventricular tumors endoscopically without major or severe complications. In young children, surgical treatment is more difficult and risky, but tumor resection should be performed as early as possible (11).

A study conducted in Slovenia on 12 patients with choroid plexus tumors (8 PPC and 4 CPC), with a mean age of 6.1 years, reveals that they represent 0.36% of all intracranial tumors. In children under the age of 15, they represent 3.69%. Of the 7 patients with PPC undergoing surgical resection, one died postoperatively of meningitis and one had a recurrence at 1.6 years postoperatively, being reoperated without further recurrence at 17.9 years after the second operation. One patient with postoperative residual tumor remained asymptomatic at 16.5 years postoperatively. In patients with CPC, only those who received adjuvant chemotherapy and craniospinal irradiation after incomplete surgical resection survived asymptomatic 6.5 years. Survival at 10 years for total choroid plexus tumors and for PPC was 73% and 100%, respectively. In Slovenia, PPCs are 2 times more common than CPCs. Surgical resection

is the treatment of choice in PPC and radiotherapy is not applied even after subtotal resections (51). Other studies find a survival rate at 1, 5, and 10 years of 90, 81, and 77%, respectively, in PPC compared to 71, 41, and 35% in CPC, respectively. Surgery was a relevant prognostic factor in both PPC and CPC and radiotherapy was associated with a higher CPC survival rate. Only 8/22 CPCs responded to chemotherapy. Recurrences after primary therapy are an unfavorable prognostic factor in CPC but not in PPC (66).

Immunohistochemical studies performed on 12 PPC and 11 CPC with a mean survival period of 4 years of 8.5 years in PPC and 5.2 years in CPC reveal that the expressiveness of cell cycle markers and MIB-1 was higher in CPC than in PPC and the expressiveness MIB-1, p53, pRB, and E2F-1 were significantly lower in patients with CPC after chemotherapy than before (68).

17. Hemangioblastoma (HBL)

HBL represents about 1-2% of all tumors and about 10% of posterior fossa tumors (70)(71). These tumors manifest mainly in the 3-5 decades of life and are more common in males. 95% of HBL are located in the posterior fossa, of which 70-80% in the cerebellar hemispheres, 10-15% in the vermis and 10% in the brainstem. Multicenter HBLs occur in about 12% of cases. They can also occur in the cervical or supratentorial bone marrow (69).

HBLs are considered benign tumors but can cause major morbidities. HBL is the most common form of Von Hippel Lindau disease (VHL), an autosomal dominant disease caused by mutations in the VHL tumor suppressor gene (72-74). This diagnosis should be considered in patients with more than one tumor or in those with tumors with an atypical location. In these cases, a CT-scan of the chest, abdomen and pelvis should be performed for any unnoticed lesions. Most cerebellar HBLs are NOT associated with VHL.

Symptoms depend on the location and size of the lesion and may include signs of cerebellar dysfunction and hydrocephalus. Significant bleeding is a rare phenomenon in this type of lesion (73).

4 types of HBL have been described:

- type 1 (6%), a simple cyst without macroscopic evidence of a wall node;
- type 2 (65%), macrocystic form, consisting of a cyst of variable dimensions with a wall node of 0.5-2.5 cm;
- type 3 (25%), solid tumor;
- type 4 (4%), predominantly solid tumor with several small cysts (73-74)

Mutations in the tumor suppressor gene (VHL gene) increase patients' risk of developing a wide variety of tumors such as retinal or CNS HBL, clear cell kidney tumor, pheochromocytoma, pancreatic neuroendocrine tumors, endolymphatic sac tumors, papillary cystadenoids. in males.

Patients with VHL are classified as (73)(74):

- VHL type 1 in which pheochromocytoma does not predominate
- VHL type 2 in which pheochromocytoma predominates. This type is subdivided into
    - a type 2A (with kidney cancer)
    - a type 2B (without kidney cancer).

Manifestations of VHL disease

1. Cerebellar and spinal HBL (in about 65% of cases)
2. retinal angiomas (approx. 60%)
3. clear bilateral or multifocal renal cell carcinomas (approximately 45%)
4. bilateral, multifocal renal cysts (approx. 45%)
5. bilateral, multifocal pheochromocytomas (about 26%)
6. epididymal cystadenomas (approximately 26%)
7. pancreatic cysts and microcystic adenomas (over 75%), pancreatic neuroendocrine tumors (17%)
8. endolymph lymphatic tumors (about 10%)

Therapeutic options for HBL

There are two basic therapeutic options for HBL: surgical resection and stereotaxic radiosurgery. If HBL has been completely resected and is not associated with VHL disease, the patient may be considered cured. In cases of cystic HBL, it is essential to remove the solid portion.

If HBL resection cannot be complete, the tumor may recur or cause a cyst to form.

As an alternative to open surgery, stereotaxic radiosurgery can be used for HBL (15). In these cases, the cure of the lesion is gradual. In cystic HBL, only the solid part of the tumor needs to be treated radiosurgically.

The main advantage of radiosurgery over neurosurgery is that this procedure is non-invasive and eliminates the risks of open surgery, in addition to requiring a much shorter hospitalization period. On the other hand, some HBLs are located in critical areas, difficult to approach surgically. In such situations, radiosurgery is a risk-free option. In patients with VHL disease, with multiple HBL in various locations, repeated stereotaxic radiosurgery has a great advantage over open surgery that exposes the patient to major risks and morbidities.

However, there are disadvantages of radiosurgical therapy:

- Radiosurgery normally takes 6 months to 1 year to remove the tumor. If the lesion is large and exerts a significant mass effect with HIC, then open surgery is the option of choice. In cystic HBL, even after aggressive radiosurgery, the tumor continues to secrete cystic fluid a few months after treatment, and if the cyst becomes very large it will require surgical evacuation.
- Radiosurgery can cause side effects due to damage to the normal brain in the immediate vicinity of the tumor.

Advanced radiosurgery systems such as CyberKnife® eliminate many of the risks of conventional radiosurgery.

18. Follow-up

MRI is a valuable postoperative investigation to detect early recurrences before they become clinically manifest.

- In patients undergoing chemotherapy for malignant lesions, MRI is used to assess response to therapy.
- The presence of a residual tumor or a recurrence with a contrast sample at 2 months postoperatively is considered a recurrence.
- Post-radiotherapy changes can mimic a tumor recurrence, so it requires a repeat of the investigation after a few weeks.

19. Conclusions

Despite the progress in neuroimaging, neuroanesthesia, microsurgical techniques and intraoperative electrophysiological monitoring, both in terms of knowledge and technological advances, posterior fossa tumor surgery still remains a surgical challenge, associated with higher morbidity and mortality than supratentorial tumor surgery. Hence, the experience of the operator is the decisive factor in improving the surgical results while a permanent collaboration between surgeon and anesthetist is an adjuvant factor.

Abbreviations

PFT – posterior fossa tumor; **MBL –** medulloblastoma; **PNET** - primitive neuroectodermal tumors; **CPP** - Choroid plexus papilloma; **CPC** - choroid plexus carcinomas; **GNB** – ganglioneuroblastoma; **HY –** hydorcephalus; **ICH –** intracranial hypertension; **ACE** - carcinoembryonic antigen; **AFP** - alpha-fetoprotein; **CT** – computed tomography; **MRI** – magnetic resonance imaging; **CSF –** cerebral spinal fluid; **PA –** pilocytic astrocitoma; **HBL –** hemangioblastoma.

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References:

1. Cushing H. Experience with the cerebellar medulloblastoma: critical review. Acta Pathol Microbiol Immunol Scand. 1930;7:1-86
2. Chang T, Teng MM, Lirng JF. Posterior cranial fossa tumours in childhood. Neuroradiology. 1993, 35(4):274-278
3. Kleihues P, Louis DN, Scheithauer BW, Rorke LB, Reifenberger G, Burger PC, Cavenee WK: The WHO classification of tumors of the nervous system. J Neuropathol Exp Neurol, 2002, 61(3):215-225
4. Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR, eds: Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. NIH Pub. No 99-4649. Bethesda: National Cancer Institute; 1999
5. Burkhard C, Di Patre PL, Schuler D, Schuler G, Yasargil MG, Yonekawa Y, Lutolf UM, Kleihues P, Ohgaki H: A population-based study of the incidence and survival rates in patients with pilocytic astrocytoma. J Neurosurg 2003, 98(6):1170-1174

6. Duffner PK, Krischer JP, Burger PC, Cohen ME, Backstrom JW, Horowitz ME, Sanford RA, Friedman HS, Kun LE: Treatment of infants with malignant gliomas: the Pediatric Oncology Group experience. J Neurooncol 1996, 28(Suppl 2–3):245-256
7. Badhe PB, Chauhan PP, Mehta NK. Brainstem gliomas-a clinicopathological study of 45 cases with p53 immunohistochemistry. Indian J Cancer. 2004;41(4):170-174
8. Yu LJ, Wu ML, Li H, Chen XY, Wang Q, Sun Y, Kong QY, Liu J. Inhibition of STAT3 expression and signaling in resveratrol-differentiated medulloblastoma cells. Neoplasia. 2008, 10(7):736-744
9. Tomoko Omura,Hiroshi Nawashiro, Hideo Osada, Katsuji Shima, Hitoshi Tsuda, Aida Shinsuke. Case Report Pilomyxoid astrocytoma of the fourth ventricle in an adult. Acta Neurochirurgca, 2008. Commentary: Coman TC, Ciurea AV
10. Ciurea AV, Coman T. Medulloblastoma–Multimodal therapy. Overview. Romanian Neurosurgery, 2005vol XII, Nr 1, pp: 17-25
11. Fouladi M, Gajjar A, Boyett JM, et al: Comparison of CSF cytology and spinal magnetic resonance imaging in the detection of leptomeningeal disease in pediatric medulloblastoma or primitive neuroectodermal tumor. J Clin Oncol, 1999, 17 (10): 3234-3237
12. Albright AL, Wisoff JH, Zeltzer PM, et al: Effects of medulloblastoma resections on outcome in children: a report from the Children's Cancer Group. Neurosurgery, 1996, 38 (2): 265-271
13. Giangaspero F, Wellek S, Masuoka J, et al: Stratification of medulloblastoma on the basis of histopathological grading. Acta Neuropathol, 2006, 112(1): 5-12
14. Packer RJ, Siegel KR, Sutton LN, et al: Efficacy of adjuvant chemotherapy for patients with poor-risk medulloblastoma: a preliminary report. Ann Neurol, 1988, 24(4): 503-508
15. Yao MS, Mehta MP, Boyett JM, et al: The effect of M-stage on patterns of failure in posterior fossa primitive neuroectodermal tumors treated on CCG-921: a phase III study in a high-risk patient population. Int J Radiat Oncol Biol Phys, 1997, 38(3): 469-476
16. Frank AJ, Hernan R, Hollander A, et al.: The TP53-ARF tumor suppressor pathway is frequently disrupted in large/cell anaplastic medulloblastoma. Brain Res Mol Brain Res, 2004, 121(1-2): 137-140

17. Gajjar A, Hernan R, Kocak M, et al.: Clinical, histopathologic, and molecular markers of prognosis: toward a new disease risk stratification system for medulloblastoma. J Clin Oncol, 2004, 22(6): 984-993
18. Ray A, Ho M, Ma J, et al: A clinicobiological model predicting survival in medulloblastoma. Clin Cancer Res, 2004, 10(22):7613-7620
19. Eberhart CG, Kratz J, Wang Y, et al.: Histopathological and molecular prognostic markers in medulloblastoma: c-myc, N-myc, TrkC, and anaplasia. J Neuropathol Exp Neurol, 2004, 63(5): 441-449
20. Grotzer MA, Hogarty MD, Janss AJ, et al: MYC messenger RNA expression predicts survival outcome in childhood primitive neuroectodermal tumor/medulloblastoma. Clin Cancer Res, 2001, 7(8): 2425-2433
21. Herms J, Neidt I, Lüscher B, et al: C-MYC expression in medulloblastoma and its prognostic value. Int J Cancer, 2000, 89(5): 395-402
22. Lamont JM, McManamy CS, Pearson AD, et al: Combined histopathological and molecular cytogenetic stratification of medulloblastoma patients. Clin Cancer Res, 2004, 10(16): 5482-5493
23. Lonergan GJ, Schwab CM, Suarez ES, Carlson CL. Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma: radiologic-pathologic correlation. Radiographics, 2002, 22:911-934
24. Rorke LB, Hart MN, McLendon RE. Supratentorial primitive neuroectodermal tumour (PNET). In Kleihues P, Cavenee WK (Eds). Pathology and genetics of tumours of the nervous system. 2.Ed. Lyon: IARC Press, 2000;141-144
25. Nakazato Y, Hosaka N. A 32-year-old man with left temporal lobe tumor. Neuropathology, 2004, 24:261-262
26. Sibilla L, Martelli A, Farina L, et al. Ganglioneuroblastoma of the spinal cord. AJNR 1995, 16:875-877
27. Tanaka M, Shibui S, Nomura K, Nakanishi Y. Pineal ganglioneuroblastoma in an adult. J Neurooncol, 1999, 44:169-173
28. Durity FA, Dolman CL, Moyes PD. Ganglioneuroblastoma of the cerebellum: case report. J Neurosurg 1968, 28:270-273
29. Kombogiorgas D, Natarajan K, Sgouros S. Predictive value of preoperative ventricular volume on the need for permanent hydrocephalus treatment immediately after resection of posterior fossa medulloblastomas in children. J Neurosurg Pediatrics. 2008 Jun;1(6):451-5
30. Arriada N, Sotelo J. Continuous-flow shunt for treatment of hydrocephalus due to lesions of the posterior fossa. J Neurosurg. Nov

2004;101(5):762-766
31. Sure U, Berghorn WJ, Bertalanffy H. Collin's law. Prediction of recurrence or cure in childhood medulloblastoma? Clin Neurol Neurosurg, 1997, 99(2):113-116
32. Roldán G, Brasher P, Vecil G, Senger D, Rewcastle B, Cairncross G, Forsyth P, Hamilton M. Population-based study of medulloblastoma: outcomes in Alberta from 1975 to 1996. Can J Neurol Sci. 2008, 35(2):210-215
33. Albright AL, Wisoff JH, Zeltzer PM, et al: Effects of medulloblastoma resections on outcome in children: a report from the Children's Cancer Group. Neurosurgery, 1996, 38 (2): 265-271
34. Robertson PL, Muraszko KM, Holmes EJ, et al: Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group. J Neurosurg, 2006, 105(6): 444-451
35. Evans AE, Jenkin RD, Sposto R, et al.: The treatment of medulloblastoma. Results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone. J Neurosurg, 1990, 72 (4): 572-582
36. Geyer JR, Zeltzer PM, Boyett JM, et al: Survival of infants with primitive neuroectodermal tumors or malignant ependymomas of the CNS treated with eight drugs in 1 day: a report from the Childrens Cancer Group. J Clin Oncol, 1994, 12(8): 1607-1615
37. Brandes AA, Ermani M, Amista P, Basso U, Vastola F, Gardiman M, Iuzzolino P, Turazzi S, Rotilio A, Volpin L, Mazza C, Sainati L, Ammannati F, Berti F. The treatment of adults with medulloblastoma: a prospective study. Int J Radiat Oncol Biol Phys. 2003, 57:755-761
38. Chang CH, Housepain EM, Herbert C Jr. An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastomas. Radiologz, 1969, 93: 1351-1359
39. Fukunaga-Johnson N, Sandler HM, Marsh R, et al.: The use of 3D conformal radiotherapy (3D CRT) to spare the cochlea in patients with medulloblastoma. Int J Radiat Oncol Biol Phys, 1998, 41 (1): 77-82
40. Huang E, Teh BS, Strother DR, et al.: Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. Int J Radiat Oncol Biol Phys, 2002, 52(3): 599-605
41. Thomas PR, Deutsch M, Kepner JL, et al: Low-stage medulloblastoma: final

analysis of trial comparing standard-dose with reduced-dose neuraxis irradiation. J Clin Oncol, 2000, 18(16): 3004-3011
42. Gajjar A, Chintagumpala M, Ashley D, et al: Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. Lancet Oncol, 2006, 7(10): 813-820
43. Oyharcabal-Bourden V, Kalifa C, Gentet JC, et al: Standard-risk medulloblastoma treated by adjuvant chemotherapy followed by reduced-dose craniospinal radiation therapy: a French Society of Pediatric Oncology Study. J Clin Oncol, 2005, 23(21): 4726-4734
44. Packer RJ, Gajjar A, Vezina G, et al: Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol, 2006, 24(25): 4202-4208
45. Ris MD, Packer R, Goldwein J, et al: Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. J Clin Oncol, 2001, 19(15): 3470-3476
46. Packer RJ, Sutton LN, Elterman R, et al.: Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. J Neurosurg, 1994, 81(5): 690-698
47. Verlooy J, Mosseri V, Bracard S, et al: Treatment of high risk medulloblastomas in children above the age of 3 years: a SFOP study. Eur J Cancer, 2006, 42(17): 3004-3014
48. Konoplia NE, Strongin IuS, Talabaev MV, Aleĭnikova OV. [Effectiveness of intensive chemotherapy in the treatment of medulloblastoma/primitive neuroectodermal tumor in children] [Article in Russian] Vopr Onkol, 2008, 54(2):157-163
49. Duffner PK, Horowitz ME, Krischer JP, et al.: Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. N Engl J Med, 1993, 328 (24): 1725-1731
50. Dupuis-Girod S, Hartmann O, Benhamou E, et al.: Will high dose chemotherapy followed by autologous bone marrow transplantation supplant cranio-spinal irradiation in young children treated for medulloblastoma? J Neurooncol, 1996, 27 (1): 87-98
51. Rutkowski S, Bode U, Deinlein F, et al: Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. N Engl J

Med, 2005, 352(10): 978-986
52. Thorarinsdottir HK, Rood B, Kamani N, et al: Outcome for children <4 years of age with malignant central nervous system tumors treated with high-dose chemotherapy and autologous stem cell rescue. Pediatr Blood Cancer, 2007, 48(3): 278-284
53. Abe M, Tokumaru S, Tabuchi K, Kida Y, Takagi M, Imamura J. Stereotactic radiation therapy with chemotherapy in the management of recurrent medulloblastomas. Pediatr Neurosurg. 2006;42(2):81-88
54. Taylor RE, Bailey CC, Robinson K, et al: Results of a randomized study of preradiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: The International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study. J Clin Oncol, 2003, 21(8): 1581-1591
55. Cangir A, van Eys J, Berry DH, et al.: Combination chemotherapy with MOPP in children with recurrent brain tumors. Med Pediatr Oncol, 1978, 4(3): 253-261.
56. Friedman HS, Oakes WJ: The chemotherapy of posterior fossa tumors in childhood. J Neurooncol, 1987, 5 (3): 217-229
57. Needle MN, Molloy PT, Geyer JR, et al: Phase II study of daily oral etoposide in children with recurrent brain tumors and other solid tumors. Med Pediatr Oncol, 1997, 29(1): 28-32
58. Viano JC, Herrera EJ, Suarez JC. Cerebellar astrocytomas: a 24-year experience. Childs Nerv Syst. 2001, 17(10):607-610
59. Malik A, Deb P, Sharma MC, Sarkar C. Neuropathological spectrum of pilocytic astrocytoma: an Indian series of 120 cases. Pathol Oncol Res, 2006, 12(3):164-171
60. Maris C, Rorive S, Sandras F, D'Haene N, Sadeghi N, Bièche I, Vidaud M, Decaestecker C, Salmon I. Tenascin-C expression relates to clinicopathological features in pilocytic and diffuse astrocytomas. Neuropathol Appl Neurobiol, 2008, 34(3):316-329
61. Figueiredo EG, Matushita H, Machado AG, Plese JP, Rosemberg S, Marino R Jr. Leptomeningeal dissemination of pilocytic astrocytoma at diagnosis in childhood: two cases report. Arq Neuropsiquiatr. 2003, 61(3B):842-847
62. McCowage G, Tien R, McLendon R, Felsberg G, Fuchs H, Graham ML, Kurtzberg J, Moghrabi A, Ferrell L, Kerby T, Duncan-Brown M, Stewart E, Robertson PL, Colvin OM, Golembe B, Bigner DD, Friedman HS. Successful treatment of childhood pilocytic

astrocytomas metastatic to the leptomeninges with high-dose cyclophosphamide. Med Pediatr Oncol, 1996, 27(1):32-39
63. Boethius J, Ulfarsson E, Rahn T, Lippittz B. Gamma knife radiosurgery for pilocytic astrocytomas. J Neurosurg. 2002, 97(5 Suppl):677-680
64. Palma L, Celli P, Mariottini A. Long-term follow-up of childhood cerebellar astrocytomas after incomplete resection with particular reference to arrested growth or spontaneous tumour regression. Acta Neurochir (Wien), 2004, 146(6):581-588
65. Graham DI, Lantos PL: Tumors of the choroid plexus. In: Graham DI, Lantos PL, eds. Greenfield's Neuropathology. Vol 2. 6th ed. New York, NY: Oxford University Press; 1997: 647-652
66. Wolff JE, Sajedi M, Brant R, Coppes MJ, Egeler RM. Choroid plexus tumours. Br J Cancer. 2002, 87(10):1086-1091
67. Rickert CH, Wiestler OD, Paulus W: Chromosomal imbalances in choroid plexus tumors. Am J Pathol, 2002, 160(3): 1105-1113
68. Carlotti CG Jr, Salhia B, Weitzman S, Greenberg M, Dirks PB, Mason W, Becker LE, Rutka JT. Evaluation of proliferative index and cell cycle protein expression in choroid plexus tumors in children. Acta Neuropathol (Berl). 2002, 103(1):1-10
69. Namiki H, Hardman MJ, Yang H. The Central Nervous System. In: Silverberg SG, Delellis RA, Frable WJ, editors. Principles and Practice of Surgical Pathology and Cytopathology. 3rd ed. Churchill and Livingstone, 1997; 2905-3036
70. Giannini C, Scheithauer BW, Hellbuch LC. Peripheral nerve hemangioblastoma. Mod Pathol, 1998, 11:999-1004
71. Parici EJ, Mena H. Nonglial Tumours. In: Nelson JS, Parisi JE, Schochet SJr, editors. Principles and Practice of Neuropathology. St. Louis: Mosby, 1993, 203-266.
72. Lonser RR, Glenn GM,Walther M, et al.Von Hippel-Lindau disease. Lancet, 2003, 361:2059–2067.
73. Richard S, David P, Marsot-Dupuch K, Giraud S, Beroud C, Resche F. Central nervous system hemangioblastomas, endolymphatic sac tumors, and von Hippel- Lindau disease. Neurosurg Rev. 2000, 23:1–22.
74. Svensson AM, Pang Y, Moore NJE, Tindle BH. Cystic Tumor of the Cerebellum Arch Pathol Lab Med, 2006, Vol 130, pp:886-889
75. Chang SD, Main W, Martin DP, Gibbs IC, Heilbrun MP: An analysis of the CyberKnife: a robotic frameless stereotactic radiosurgical system. Neurosurgery. 2003, 52(1):140-147

CEREBRAL METASTASIS

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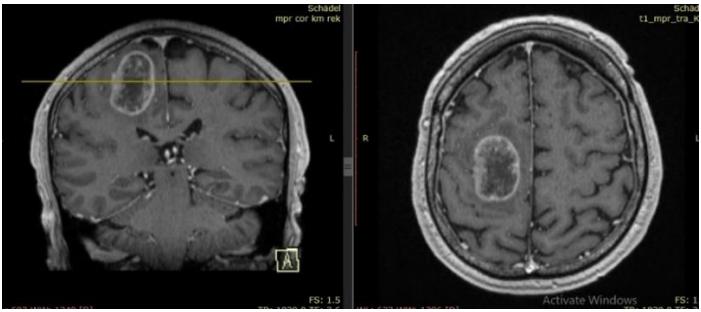

Figure 1. MRI - Bronhopulmoary neoplasm metastasis
(Personal collection of dr. Vicențiu Săceleanu)

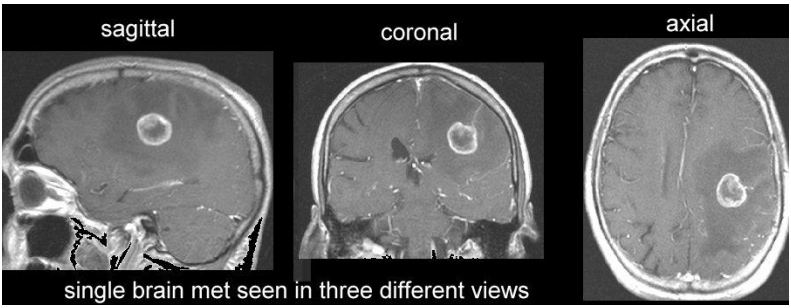

Figure 2. MRI - single brain metastasis
(Personal collection of dr. Vicențiu Săceleanu)

Brain metastases (Figure 1,2) are secondary dissemination of some carcinomas located in other areas of the body, the most common being the lung, breast, melanoma, renal cell carcinoma. There have been described three types:

a. *Skull bone and dura mater metastases* are common in lung and prostate carcinomas. Cranial convexity metastatic tumours are usually asymptomatic, but those of the base may damage the cranial nerves tract or the pituitary gland.

Diagnosis is made after skull radiography (Hirtz position) and cranial CT with bone window.

b. *Brain metastases* reach this level through the marrow. Approximately one third come from the lung, followed by the breast, melanomas, carcinomas of the gastrointestinal tract (stomach, colon, rectum).

In over 70% of cases, metastases are multiple, both in the brain, and the cerebellum, and can be synchronous or metachronous in relation with the initial tumour process. They are often located close to the surface in the subcortical white matter. Their shape is circumscribed, rarely cystic surrounded by local vasogenic edema (Figure 3)

The clinical features of the metastatic carcinoma of the brain are similar to that of glioblastoma multiforme. The most common manifestations are represented by headache, focal motor deficit, behavioural abnormalities, seizures, ataxia, aphasia and signs of intracranial hypertension, all of them with a fast and progressive evolution.

c. *Meningeal carcinomatosis* is about 4% of brain metastases and derives from adenocarcinomas of the breast, lung, gastrointestinal tract, melanoma and leukemia. The main manifestations are represented by headache, cervicalgia, radicular pain, paralysis of cranial nerves, dementia. Approximately 50% of patients have hydrocephalus. CSF examination shows an increase of proteinorahia and glycorrhachia. The treatment consists of radiotherapy followed by methotrexate or cytarabine administration . Survival after the diagnosis is of several weeks or months. The method of choice in the diagnosis of brain metastasis is the cranial CT scan and MRI, on which it appears as round,

small, hyper, hypo or isodense areas surrounded by intense perifocal edema located at cortical-subcortical level. (Figure 3,4)

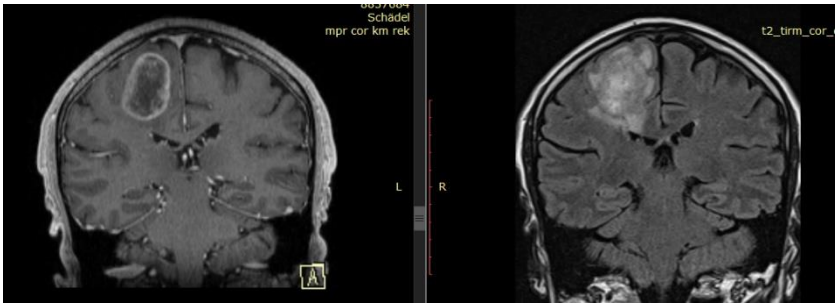

Figure 3. MRI. Lung cancer unique brain metastasis
(Personal collection of dr. Vicențiu Săceleanu)

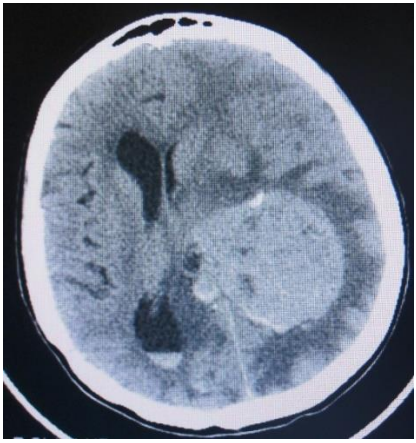

Figure 4. Malignant melanoma mestastasis
(Personal collection of dr. Vicențiu Săceleanu)

Tumour density increases markedly after the administration of contrast. An important feature is the fact that they can be multiple. Lumbar puncture, simple thoracopulmonary radiography can also be performed, ESR (elevated in 70% of metastatic carcinomas but not in glioblastomas).

MRI with contrast is mandatory because it detects the lesions that were not visible on CT scan.

Treatment. If there are no signs of metastatic tumour in other organs, it is a single metastasis and the patient is in good general condition, neurosurgical excision can be performed followed by radiation and chemotherapy. (figure 4) If there are multiple but grouped metastases that can be excised during the same operating time, then surgery is performed. For the multiple metastases, irradiation followed by steroid therapy can bring a slight improvement.

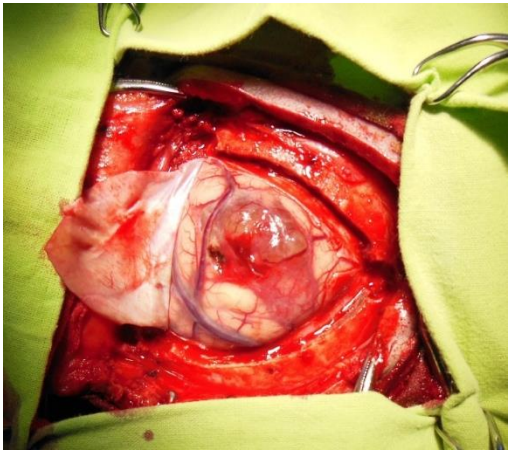

Figure 4. Brain pulmonary metastasis
(Personal collection of dr. Vicențiu Săceleanu)

Despite these therapeutic measures, survival is only slightly prolonged, prognosis is reserved and dictated by the biological status of the patient and the surgical cure of the primary tumour. The average length of survival in the patients with treatment is of 6 months.

Case Presentation

28-year-old, male, young doctor, came at the hospital in 2009 blaming motor aphasia. Cerebral MRI Scan: left temporal lobe tumor.

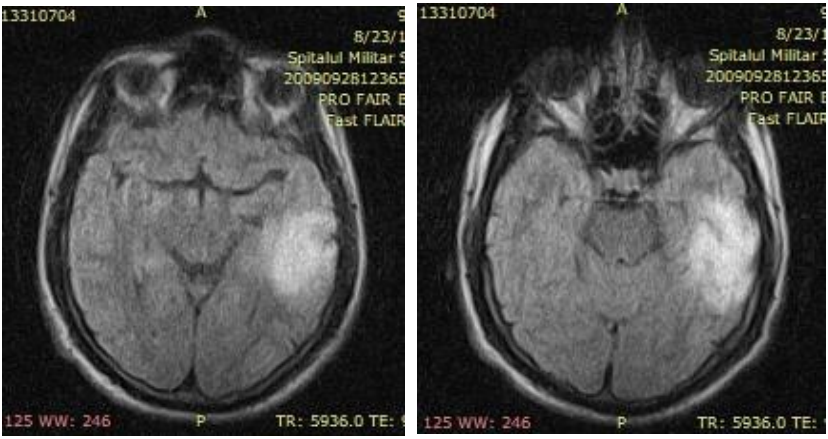

Figure 1. 2009 Oligodendroglioma grade II
(Personal collection of dr. Vicențiu Săceleanu)

After neurosurgical ablation, the anatomopathological result: Oligodendroglioma Grade 2 (low-grade). In the high ranked neurosurgical centers, life expectancy of patients diagnosed with oligodendroglioma grade 2 is of 12 years. (3)

In oligodendrogliomas grade 2, radiotherapy is not beneficial and chemotherapy is not mandatory (4). Patient chooses to continue without these alternative therapies, but with frequently imaging controls. Every 6 or 12 months a MRI with contrast: no tumor recurrence, asymptomatic. The patient can practice his job without impairment.

In 2016, after a seizure, the MRI shows a tumor recurrence.

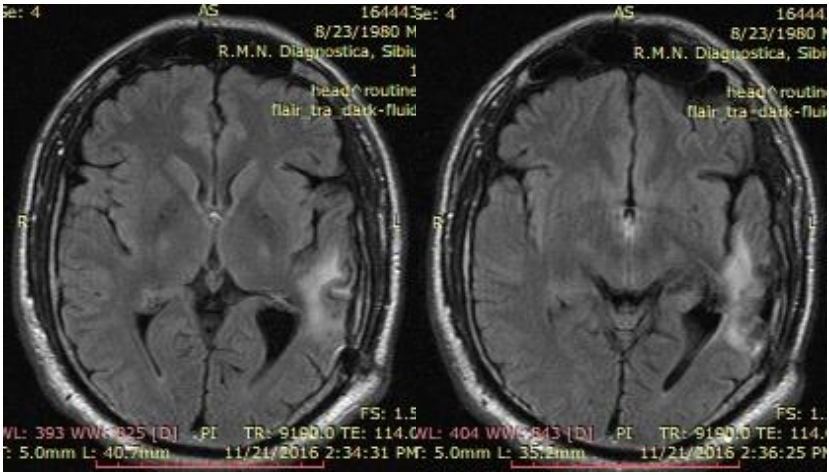

Figure 2. 2016 Oligoastrocitoma grade III (2007 WHO Classification) (Personal collection of dr. Vicențiu Săceleanu)

After neurosurgical ablation of the tumor, histologically 2 biphasic tumors of the oligodendrolyal and astrocytar type was identified. The diagnosis: grade III Oligo-astrocitoma (based on 2007 WHO classification) (5)

After surgery, the patient was subjected to radiotherapy and chemotherapy. Even the introduction of temozolomide in radiation treatment was an important advance, in recent studies different agents combinations have been used for the recurrent and progressive supratentorial treatment of high-grade astrocytomas. The results have been quite disappointing. Response rates are low and progression time is short. (6)

Statistically, the life expectancy at the 1st diagnosis time, in the case of grade III oligoastrocitoma is 3.5 years.(7)

In 2017 the control cerebral MRI with iv contrast reveals a cerebral gliosis area, without tumorous areas. No neurological symptoms. The patient continues to practice his profession.

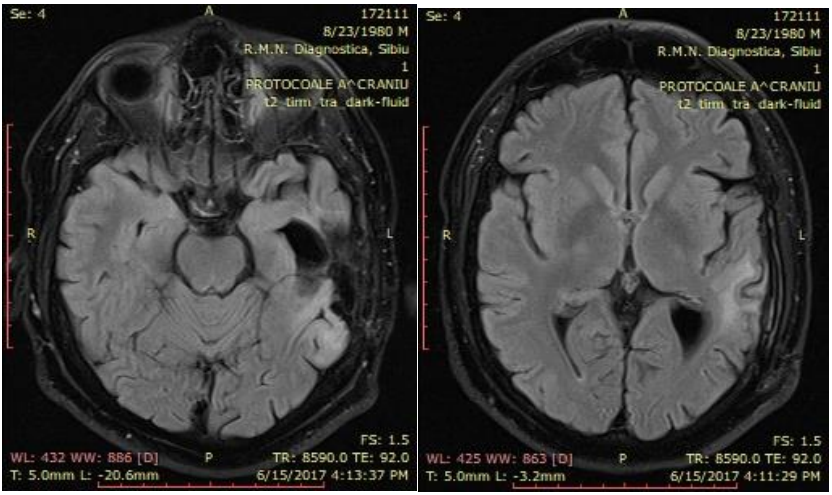

Figure 3 MRI aspect 2017
(Personal collection of dr. Vicențiu Săceleanu)

In 2018, following the usual cerebral MRI exam, an important tumour recurrence is identified.

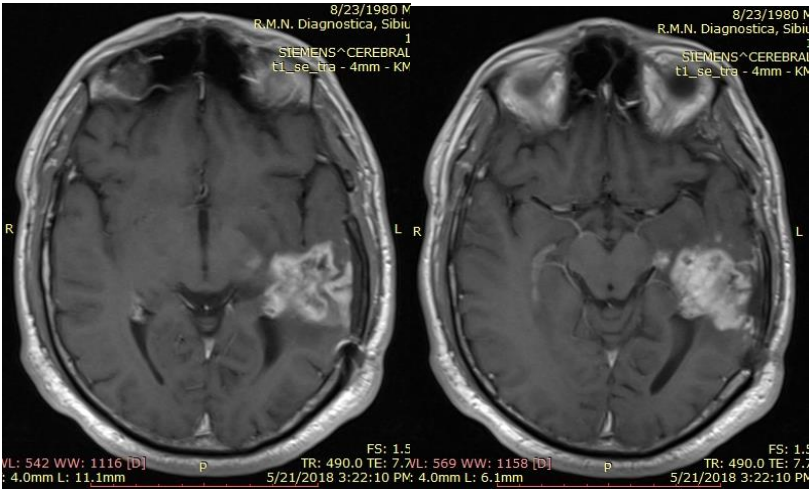

Figure 4. 2018 Glioblastoma Before Surgery
(Personal collection of dr. Vicențiu Săceleanu)

After another surgical ablation, the diagnosis was: IDH wild-type glioblastoma. It was performed a genetical testing for the first time. In IDH Wild-type Glioblastoma life expectancy is 11-13 months.(8) Surprisingly, in the literature, IDH Wild-Type GBM is described as a primary tumour, which develops without precursor ("de novo").

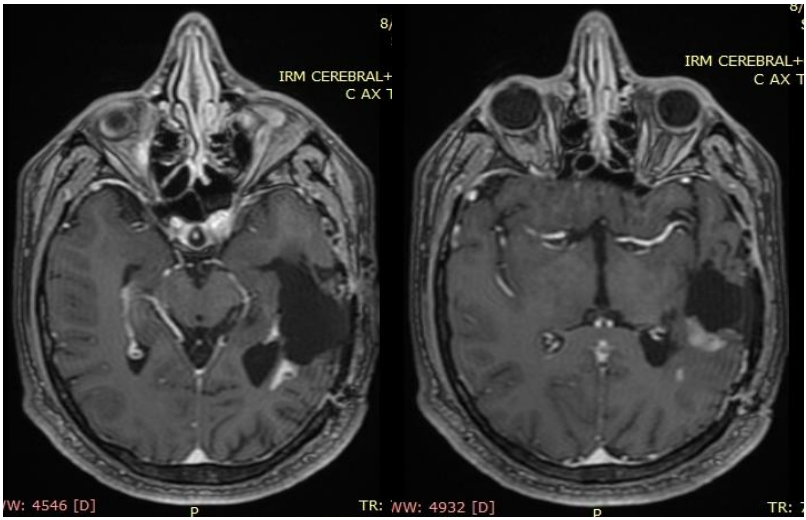

Figure 5. 2018 Glioblastoma After Surgery
(Personal collection of dr. Vicențiu Săceleanu)

In 2019, the patient came at the hospital with aggravated symptoms: right hemiparesis, headache, motor aphasia.

On the MRI it was identified a huge tumor recurrence, with extension in deep structures: basal ganglia, cerebral peduncles and mesencephalon.

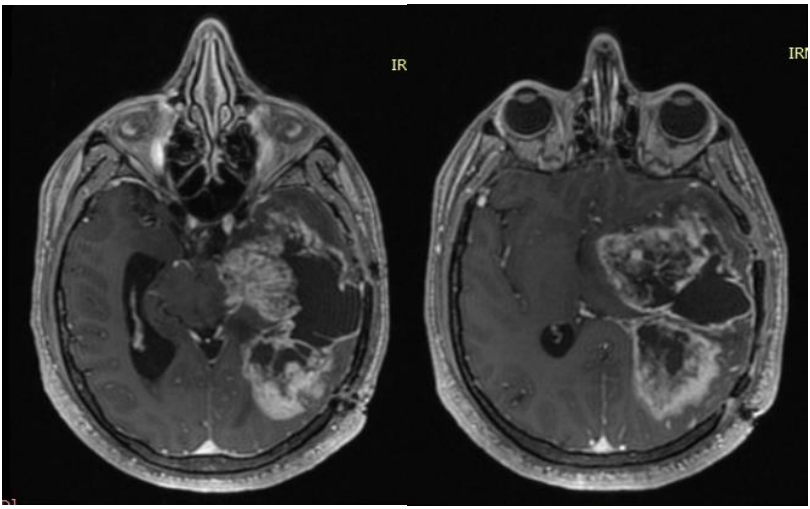

Figure 6. 2019 Glioblastoma Before Surgery
(Personal collection of dr. Vicențiu Săceleanu)

Neurosurgical intervention is done with a subtotal ablation of the tumor, to preserve the main neurological functions, at the patient's choice.

After surgical recovery, the neurological functions are slightly improved.

Patient finish his battle 3 months later, at:

- 10 years and 6 months after his first surgery (oligodendroglioma grade II);
- 3 years and 6 months from second surgery (oligoastrocytoma grade III);
- 1 year and 3 months from his third one (glioblastoma grade 4).

Discussions

The cause of central nervous system gliomas is unknown. Cerebral gliomas cannot be prevented. (9)

There are many studies with conduct environmental, occupational, family, and genetic research to identify common links between patients. Most brain tumors are not hereditary. Only 5% of brain tumors can

occur in a genetically inherited context, such as Neurofibromatosis, Li-Frameni, Von HippelLindau, Turcot and Tuberculous Sclerosis. (10)

In the case previous presented we can discuss certain questions:

- Was the first tumor, oligodendroglioma grade II, cured after tumour resection? We can discuss considering that for 7 years all MRI checks did not show any local tumour recurrence.
- In the second histopathological result, two distinct tumour lines were identified, of oligodendrocytes and astrocytes, making the diagnosis at that time, according to the WHO 2006 classification, of Oligoastrocytoma grade 3. After the WHO 2016 classification we can discuss the coexistence of two tumours, grade 3 astrocytoma and oligodendroglioma.

In 2016 WHO changed the classification based on the genetical testing. No more oligoastrocitoma, can be oligodendroclioma, astrocytoma or both. (12)

- Glioblastoma IDH - wild-type is described in the literature primarily as a primary brain tumor. Mutant IDH glioblastoma is the one that occurs most frequently by escalation from a lower grade glioma.(13)

This may raise questions about the accuracy of the genetic test or the impact of radiation therapy in the development of wild-type glioblastoma. We already know from Prof. Hugues Duffau studies that the use of radiotherapy in low-grade gliomas is totally contraindicated.

An important role in the pathophysiology of cerebral gliomas has been identified in the metabolism of thrombin generation. In patients with cerebral gliomas, high thrombin generation values were identified. This was also identified in the case of the patient in this case presentation. The use of thrombin inhibitors in the treatment of cerebral gliomas may be tested in the future.(14) Research in the field of medication delivered through nanoparticles should be followed, which can have important results in the future treatment of this pathology. (15)

Conclusions

Surgical treatment is not curative in brain gliomas, even in the case of very early discoveries. Surgerical ablatia is important to obtain a

tumor biopsy for histopathological analysis, cytoreduction of tumor mass with the reduction of the symptoms caused by the presence of tumor. The decrease in tumor volume also decrease the progression of the disease.

Ideally, the surgeon wants to completely excise the tumor, even supramarginal. But, due to the location of the tumor and the eloquent areas involved, some tumors cannot be completely removed because this would be done with the cost of neurological deficit.

In the multitude of current research, medical experts tries all possible approaches: radiotherapy, various combinations of chemotherapy, gene therapy, immunotherapy, stem cells, biomarkers, but looking at the whole picture it seems that we are in a chaotic stage.

In the previous presented case, a doctor honourably practiced his medical activity with a cerebral glioma in his head. This proves to us that even with the current reduced therapeutic means, with a good management of the case we can offer beautiful years of life to our patients.

References:

1. Wesseling P, C. D. (2018). WHO 2016 Classification of gliomas. *Neuropathology and Applied Neurobiology 44*, 139-150.
2. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131(6):803-820.
3. Claus EB, Walsh KM, Wiencke JK, et al. Survival and low-grade glioma: the emergence of genetic information. Neurosurg Focus. 2015;38(1):E6.
4. Duffau H, Taillandier L. New concepts in the management of diffuse low-grade glioma: Proposal of a multistage and individualized therapeutic approach. Neuro Oncol. 2015;17(3):332-342.
5. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system [published correction appears in Acta Neuropathol. 2007 Nov;114(5):547]. Acta Neuropathol. 2007;114(2):97-109.
6. Merrell, R. T., Quant, E. C., & Wen, P. Y. (2010). Advances in Treatment Options for High-grade Glioma—Current Status and Future Perspectives. US Neurology, 06(01), 55.

7. Walid MS. Prognostic factors for long-term survival after glioblastoma. Perm J. 2008;12(4):45-48.
8. Tamimi AF, Juweid M. Epidemiology and Outcome of Glioblastoma. In: De Vleeschouwer S, editor. Glioblastoma. Brisbane (AU): Codon Publications; 2017 Sep 27. Chapter 8.
9. Săceleanu V. Neurochirurgie Clinică, Edit. ULBS Sibiu; 2014.
10. Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee ShU. Glioblastoma Multiforme: A Review of its Epidemiology and Pathogenesis through Clinical Presentation and Treatment. Asian Pac J Cancer Prev. 2017;18(1):3-9.
11. Gîță, I. E. (2016). Implications for language acquisition theories: a fresh look at the "genie case". Revista Transilvania(12), 57-60.
12. Kobyakov GL, Absalyamova OV, Poddubskiy AA, Lodygina KS, Kobyakova EA. Klassifikatsiia VOZ pervichnykh opukholeĭ tsentral'noĭ nervnoĭ sistemy 2016 g.: vzgliad klinitsista [The 2016 WHO classification of primary central nervous system tumors: a clinician's view]. Zh Vopr Neirokhir Im N N Burdenko. 2018;82(3):88-96.
13. Huang J, Yu J, Tu L, Huang N, Li H, Luo Y. Isocitrate Dehydrogenase Mutations in Glioma: From Basic Discovery to Therapeutics Development. Front Oncol. 2019;9:506.
14. Cindea, C., Mihaila, R. and Saceleanu, V., 2019. Thrombosis Generation Abnormalities In Spontaneous Intracerebral Haemorrhage. Romanian Neurosurgery, 33.
15. S. Cavalu et al., Eco-friendly, Facile and Rapid Way for Synthesis of Selenium Nanoparticles production, structural and morphological characterisation. Revista de Chimie, 2017. 68(12): p. 2963-2966
16. Ciurea AV. Tumori cerebrale la copii. In: Nicolau S., Popa I (sub red.), Probleme actuale în Pediatrie, Vol.V, Oncologie generală și oncopediatrie, Edit.Helocon, Timișoara, 1999.
17. Ciurea AV. Tumorile intracraniene. In: Angelescu N. (sub.red,), Tratat de Patologie Chirurgicală, Edit.Medicală, 2001.
18. Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk AM, Hill MD, Patronas N, Latour L, Warach S. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet 2007; 369: 293-298.

19. Cochrane DD, Kestle JR. The influence of surgical operative experience on the duration of first ventriculoperitoneal shunt function and infection.Pediatr. Neurosurg., 2003.
20. Compagnone C, Murray GD, Teasdale GM, Maas Al, Esposito D, Princi P, et al. The management of patients with intradural post-traumatic mass lesions: a multicenter survey of current approaches to surgical management in 729 patients coordinated by the European Brain Injury Consortium. Neurosurgery 61:1 Suppl232–241, 2007.
21. Costache M. Anatomia Omului – vol IV, V, Sibiu 2005.
22. Dănăilă L. Vascularizația arterială și venoasă a creierului, 2001.
23. Dănăilă L, Adam D. Sinteze Neurochirurgicale, Edit.Ceres, București, 2001.
24. Dănăilă L, Carp N, Arsene D. Clinica și morfologia proceselor expansive ale sistemului nervos central, Edit.Universitară Carol Davila, București, 2005.
25. Florian lSt. Neurochirurgie. Curs pentru studenți, Cluj-Napoca, Edit.Srima, 2003.
26. Ciurea AV. Tratat de Neurochirurgie, vol. 1, Edit. Medicală, București, 2010.
27. Ciurea AV. Tratat de Neurochirurgie, vol.2, Edit. Medicală, București, 2011.

INTRODUCTION TO CRANIAL APPROACHES IN NEUROSURGERY

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Timendi causa est nescire (lat. Ignorance is the cause of fear)
Seneca, Naturales quaestiones, 65 A.D.

Contents

1. General craniotomy techniques

To obtain favorable results, any neurosurgical intervention involves a sequence of procedures that must be followed step-by-step. In general, surgical flaps involve the following steps:

1. **Preoperative planning**
   - Complete paraclinical examination: complete blood tests, imaging (Rx, CT-scan, MRI, angiography

and EEG and EMG if necessary) for exact localization of the lesion,

- Determine if unilateral or bilateral approach
- Enema, no food for at least 8 hours before surgery
- Minimal shave: 3-cm-wide strip along planned incision with disposable razor

2. **Anesthesia**
   - General anesthesia, orotracheal intubation
   - The anesthesiologist must be informed about the level of intracranial pressure
   - Constant blood-pressure monitoring through arterial line
   - Hyperventilation to P_{CO_2}=25-30mmHg
   - IV antibiotics, dexamethasone, seizure prophylaxis preoperatively; mannitol (0.5-1g/kg) at time of incision
3. **Positioning**
   - Head is fixed with three-point Mayfield holder, (Figure 1)
   - Operating area is centered on the lesion
   - Skin pressure points are padded carefully
4. **Antiseptic scrub and surgical field preparation**
   - With sterile gloves on, betadine solution is thoroughly applied to the skin
   - Incision is marked with sterile marker
   - 4 sterile towels are placed around the marked incision; can be fixed to the skin
   - Sterile drape is placed over the patient
   - Lights are centered on the operating area
5. **Skin incision**
   - Incision is infiltrated with 0.5% lidocaine with epinephrine for better bleeding control

- Skin incision: scalpel, surgical forceps, bipolar cautery, suction, sterile gauze (the incision is realized in a step-by-step fashion for a good bleeding control)
- Raney clips are applied to skin edges except for posterior fossa approaches where adequate hemostasis requires cauterization of major scalp vessels and the use of retractors offer a better wound healing

6. **Scalp flap**
   - Using a blunt periosteal elevator, the periosteum is reflected from the bone to prepare the area for the following burr holes
   - A large portion of vascularized periosteum is harvested for later use in case duroplasty or sinus repair is necessary
7. **Burr holes**
   - Burr holes with drill (hemostasis obtained with wax)
   - Burr holes are connected using Gigli saw, handles and Gigli saw guide (wax is applied to the bone margins for hemostasis)
   - Bone dust is obtained from the wound to be used in closure
   - Bone flap is elevated, and dura mater is stripped using a wide spatula
   - Holes are drilled for dural tenting sutures and for bone fixation later
   - Cottonoids are placed epidurally along edges for better bleeding control
8. **Dural opening**
   - Dura mater is incised with dural scalpel and suspended with suture
   - Bipolar cautery is avoided to avoid dural shrinkage
   - Wet sponges and towels are placed along craniotomy edges

9. **Cerebral area identification**
   - The lesion should be in the centered and identified (EEG, fMRI, MRI, intraoperative echography, neuronavigation)
10. **Lesion ablation**
   - Operating microscope is mandatory for better visualization and hemostasis (lesion margins are easier to identify and vascular clips cannot be otherwise used)
11. **Hemostasis**
   - Bipolar cauterization, Gelaspon, Surgicel, Vivostat, arterial blood pressure is elevated to normal levels to observe any remaining bleeding sites, room-temperature saline serum is used for irrigation and hemostasis
12. **Dural closure**
   - Dura is closed with 4.0 silk sutures
   - Irrigation with room-temperature saline serum to fill the subdural space and assess watertight closure
   - Any remaining gaps in dure must be repaired with muscle or pericranium (duroplasty)
13. **Bone flap repositioning**
   - Bone flap is repositioned and secured with titanium microplates
   - Any remaining holes are filled with the bone dust collected before or with osteogenic biomaterials
14. **Epidural drain**
15. **Scalp suture in 2 anatomic layers**
16. **Sterile dressing and head wrap**
17. **Intensive care supervision**
   - Postoperative monitorization of biological constants and neurological status
   - Arterial blood pressure, pulse, diuresis, respiratory functions
   - Constant neurological evaluation, preferably every 2 hours

- Control CT-scan after maximum 24 hours
- Antibiotics, anticonvulsants, antiemetics, laxatives if necessary

18. **Drainage tube removal**
    - After 24h and replacement of the wound dressing
19. **Antibiotic treatment**
    - For 3 days or according to the pathology
20. **Discharge**
    - The patient must have access to kinesitherapy and postoperative mobilization as soon as possible
    - A treatment is prescribed according to the pathology
    - A follow-up plan is formulated
    - Socio-profesional integration as soon as possible

Equipment

- Mayfield 3-pin head holder
- Scalpel, needle forceps, needle holder, surgical forceps, hemostasis forceps, needles, surgical threads, suction
- Cavitron Ultrasonic Surgical Aspirator (CUSA)
- Hemostatic forceps, Kocher forceps, clips, retractors
- Bipolar and monopolar electrocoagulation
- Sterile gauze with oxygenated water and saline solution
- Periosteal elevator
- Hudson trephine, wax, cottonoids with saline solution
- Farabeuf retractors
- Curette, dissectors, elevators
- Craniotome, high-speed drill (Figure 4, 5, 6)
- Gigli saw with handles and conductor
- Kerrison and Dahlgren bone rongeur
- Spatulas
- Dura scalpel, dura hook and dura scissors
- Yasargil-Layla retractor system

- Operating microscope (Figure 2)
- Operating glasses with magnification
- Microsurgery kit (Figure 7)
- Vascular clips
- Drain tube
- Hemostatic materials: room-temperature saline solution, gelaspon, surgicel, vivostat (Figure 3)
- Sterile gauze, towels, cottonoids

Complications

1. **Positioning**
   - Blindness
   - Brachial plexus neuropathies
   - Tegument atonia
   - Skin perforations when fixating the head
   - Loosening of the head holder
   - Air embolism
   - Deep vein thrombosis
   - Bone fracture when fixating the head
   - Pulmonary thromboembolism
2. **Skin incision**
   - Necrosis
   - Facial paralysis
   - Scalp anesthesia
   - Esthetic
3. **Bone flap**
   - Cerebral trauma
   - Dural fistula
   - Sinus lesions
   - Air embolism
   - Opening of paranasal sinuses or mastoid cells
4. **Hemostasis**
   - Subgaleal hematoma
   - Epidural hematoma
   - Subdural hematoma

5. **Closure**

- Postoperative hemorrhage
- CSF fistula (watertight closure)
- Suture dehiscence
- Infection
- Unstable bone flap
- Postoperative headache

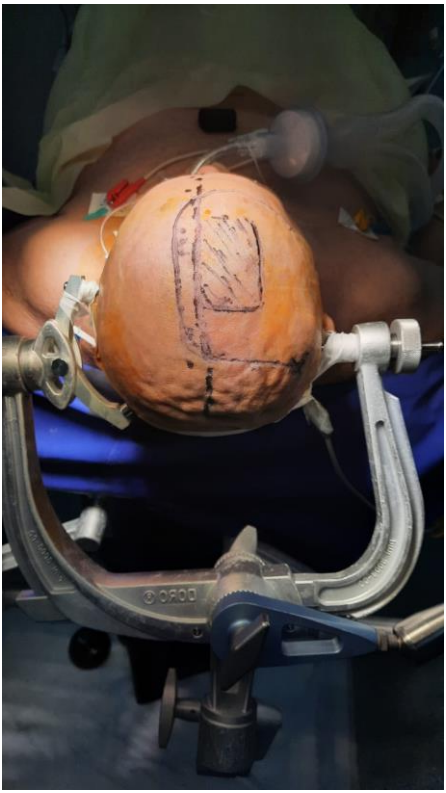

Figure 1. Head is fixed with three-point Mayfield holder (Personal collection of Prof. dr. A. V. Ciurea)

Figure 2. Operating microscope
(Personal collection of Prof. dr. A. V. Ciurea)

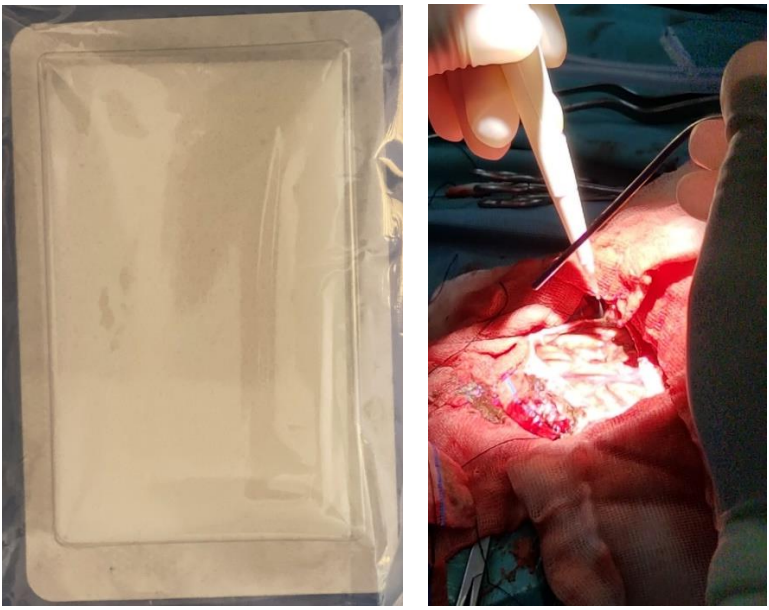

Figure 3. Hemostatic materials
(Personal collection of Prof. dr. A. V. Ciurea)

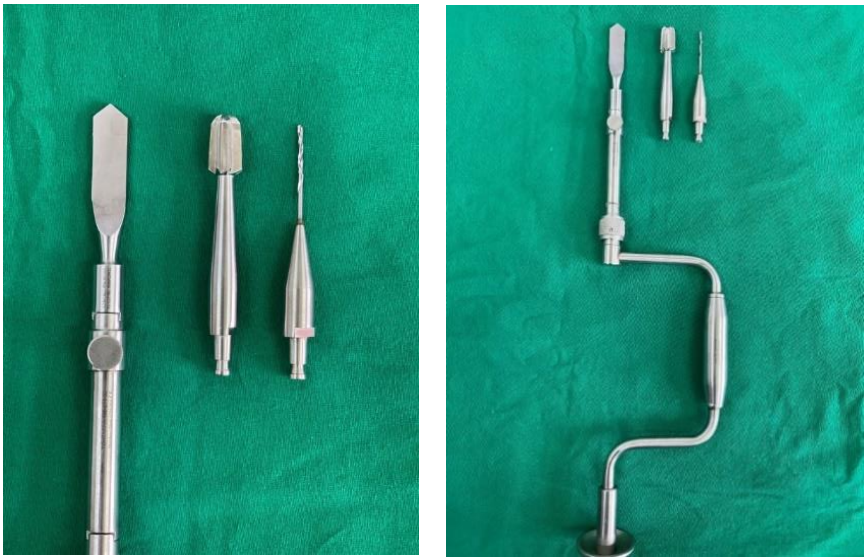

Figure 4. Hudson Trephine with Cushing bit and drill bit
(Personal collection of dr. Vicențiu Săceleanu)

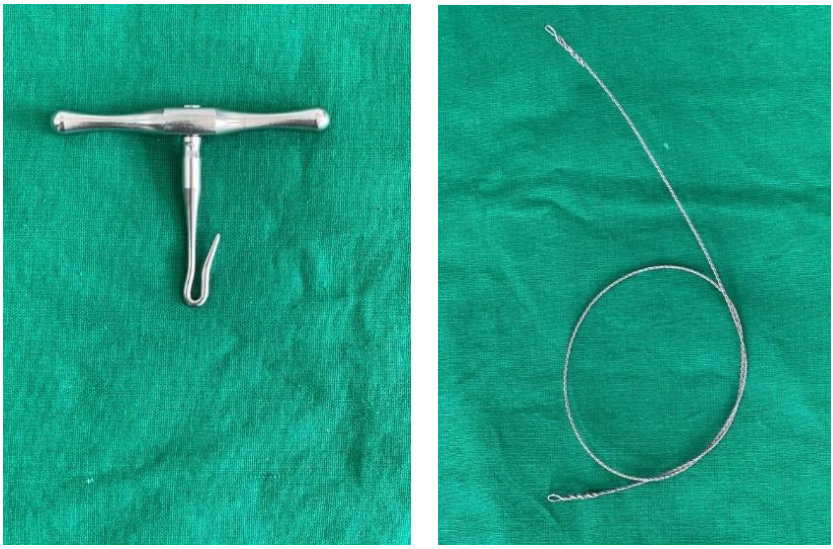

Figure 5. Gigli saw and handle
(Personal collection of dr. Vicențiu Săceleanu)

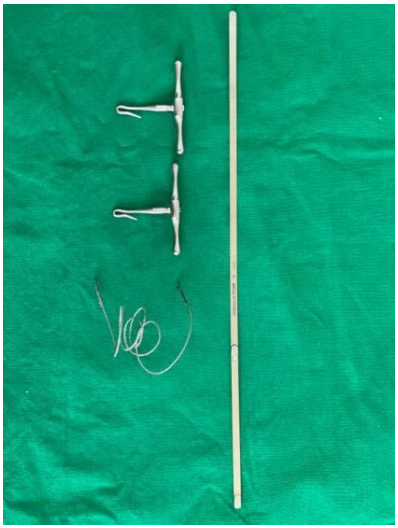

Figure 6. Gigli saw conductor *Figure 4. Craniotome*
(Personal collection of dr. Vicențiu Săceleanu)

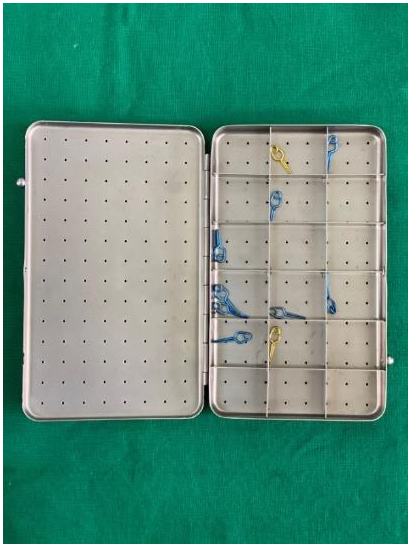

Figure 7. Aneurysm clipping kit with Yasargil microsurgery instruments
(Personal collection of dr. Vicențiu Săceleanu)

2. Burr holes

The trephine is a surgical instrument used for small bone resections necessary for the neurosurgical treatment in all cerebral pathologies.

A bone flap is obtained through the connection of multiple burr holes using a Gigli saw.

Today, the manual trephine is replaced by the modern craniotome and drill. This allows for a shorter operative time and reduces some of the complications of bone resection near the venous sinuses. (Figures 8-13)

Indications

- Chronic subdural hematoma
- Epidural hematoma
- Subdural hygroma
- Hydrocephaly
- Abscesses
- Biopsy
- Measurement of intracranial pressure

Complications

- Hemorrhage
- Infection
- Cerebral lesions
- Wrong topography
- Large blood vessels lesions
- Dural fistula
- Wound dehiscence/necrosis

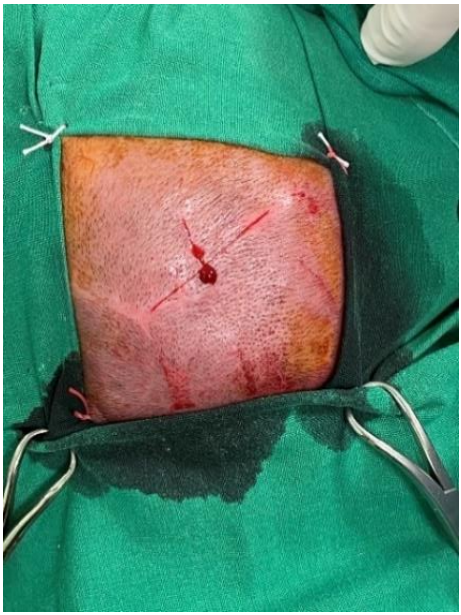

Figure 8. Betadine is used for sterile scrubbing of the scalp and 4 sterile towels secured to the skin are used to drape the operating area. The incision is infiltrated with 0.5% lidocaine with epinephrine. The scalp is cut full thickness including galea aponeurotica and pericranium down to the bone with scalpel.
(Personal collection of dr. Vicențiu Săceleanu)

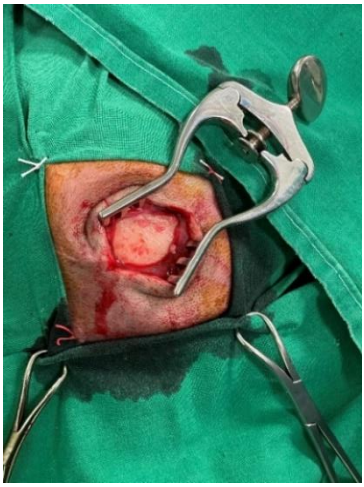

Figure 9. The remaining scalp is bluntly dissected with a periosteal elevator. A retractor is used to keep the bone exposed for the trephine. (Personal collection of dr. Vicențiu Săceleanu)

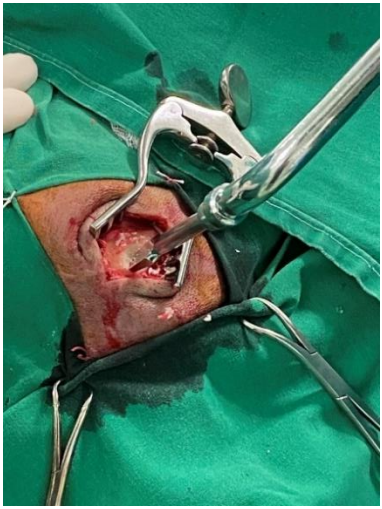

Figure 10. A Hudson trephine with a bone perforator bit is used to perform the first part of the burr hole. The trephine is applied with gentle, but steady pressure until the skull is perforated. (Personal collection of dr. Vicențiu Săceleanu)

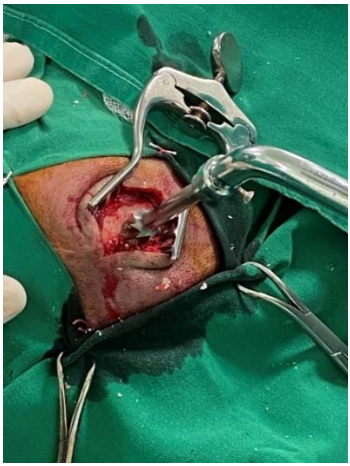

Figure 11. The perforator bit is replaced with a conical bit. The same technique is used as before until the trephine blocks itself. This means that the periosteal layer of the dura mater has been reached. All bone dust is collected for closure.
(Personal collection of dr. Vicențiu Săceleanu)

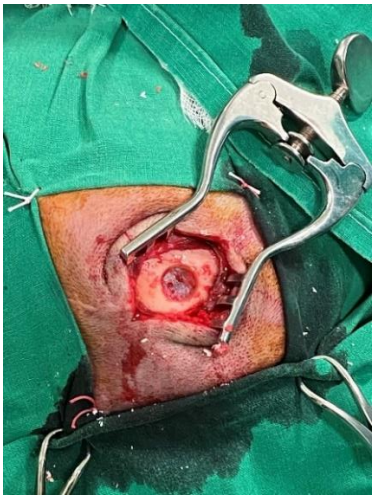

Figure 12. The trephine is removed, and the periosteal layer of the dura mater is exposed. Saline solution is used for irrigation.
(Personal collection of dr. Vicențiu Săceleanu)

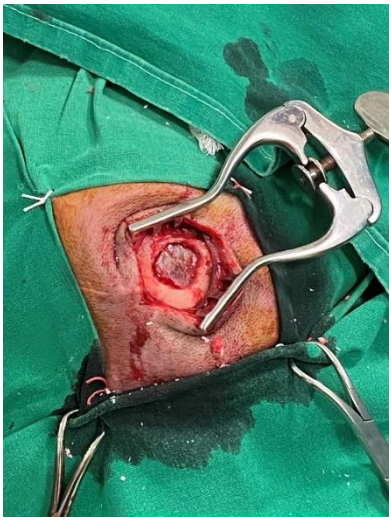

Figure 13. A curette and rongeur is used to enlarge the burr hole. (Personal collection of dr. Vicențiu Săceleanu)

3. Frontal approach

Anatomy

Delimitation of the frontal region:

- **Anterior:** glabella and the supraorbital margins of the frontal bone, which divide it from the facial area of the head
- **Lateral:** superior temporal line which divide it from the temporal region
- **Posterior:** continued by the parietal region at the level of the coronary suture
- **Medial:** the medio-sagital line, which corresponds to the superior sagittal sinus, divides it from the other frontal region

Stratigraphy

1. **Skin** – is relatively thick and has hair follicles, except for the forehead area. The forehead skin has vertical groves especially in the glabella region or transversal groves for facial expressions; in time they become deeper and permanent in elderly.

2. **Subcutaneous layer –** conjunctive fivers, very little fat tissue, epicranial aponeurosis

3. **Muscles and aponeurosis** – formed from the epicranial aponeurosis (galea aponeurotica) and fronto-occipital and temporo-parietal muscles that insert on it. This elements from a "helmet" that cover the calvarium.

Those 3 layers form the scalp. It contains numerous superficial neuro-vascular elements which are situated mainly in the subcutaneous layer. For this reason, the frontal region`s wounds are so hemorrhagic.

- **Arteries:** supratrochlear and supraorbital artery, branches from the ophthalmic artery and frontal branch of the superficial temporal artery
- **The veins** follow the arteries and form a rich vessel network which drain to the diploic veins and afterwards to the dural sinuses or extracranial veins
- **The lymphatic vessels** descent anteriorly to the submandibular ganglia
- **Nerves** – sensitive (ophthalmic nerve VI) and motor (facial nerve VII)

4. **Subaponeurotic layer** – soft connective tissue which offers some mobility for the overlying layers

5. **Pericranium** – low adherence to the calvarium bones, but strong adherence to the cranial sutures. For this reason, the cephalhematoma is limited to the contours of the cranial sutures and remains contained over a single calvarium bone.

6. **Bone** – the 2 halves of the frontal bone are protected by the metopic suture. The newborns have the bregmatic fontanelle situated between the frontal and parietal bones. It closes after 2 years. Underneath it is the superior sagittal sinus. The two tables of the skull and the diploe are traversed by the diploic veins and emissary veins that connect the dural sinuses to the extracranial veins. Their presence favors the propagation of exocranial insufficiency to endocranial insufficiency. This in turn leads to meningoencephalitis and thrombophlebitis of the dura mater sinuses.

7. **Dura mater** is the last layer and has a strong adherence to the cranial sutures, otherwise can be easily elevated. On the midline is traversed by the superior sagittal sinus.

The frontal lobe has a medial interhemispheric surface bordering falx cerebri, a lateral convex surface, a basal or inferior surface situated in the anterior fossa, a superior and a inferior margin and an anterior extremity that forms the frontal pole. Posteriorly, the frontal lobe continues with the parietal lobe.

The 3 surfaces of the frontal lobe are made up of gyri surrounded by sulci (the larger sulci are called fissures), creating the characteristic folded aspect of the human brain. The central sulcus (or fissure of Rolando) separated the frontal lobes from the parietal lobes, the Sylvian fissure separates the frontal and parietal lobes from the temporal lobes. These 2 fissures divide the frontal lobe in F1, F2 and F3 frontal areas, prefrontal gyrus, and the rectus gyrus on the inferior surface. Vascularization if realized by the anterior cerebral arteries which are in a close contact with the medial surface of the frontal lobe and branches from the medial cerebral arteries for the convex surface of the lobe.

Indications

1. Lesions of the frontal lobe (tumors, traumatic lesions, etc.)
2. Ethmoid cerebrospinal fluid fistula repair
3. Hypothalamic tumors
4. Resection of epileptic areas
5. Sella area tumors (e.g., meningiomas, craniopharyngiomas)

Preoperative planning: see general craniotomy techniques

Equipment: see general craniotomy techniques

Anesthesia: see general craniotomy techniques

Positioning

- Patient supine, left shoulder elevated, head turned 20-40° to opposite side of lesion if the approach is unilateral or median if bilateral approach
- Head elevated and neck flexed slightly

- Special care must be taken to ensure all areas of the body are sufficiently padded to ensure no skin lesion will be formed, especially if the surgery is anticipated to be long.

Antiseptic scrub and surgical field preparation: see general craniotomy techniques

Incision planning

Using sterile markers, the skin is marked for incision. At this stage, neuronavigation can be used by the surgeon according to the pathology. In general, tumors require more frequently the use of neuronavigation than vascular lesions. (Figure 14, 15)

Unilateral approach

- Arcuate incision starting from 1 cm anterior to the tragus, above the zygoma, curving superiorly the anteriorly towards the frontal midline. The incision always remains behind the hair line.

Bilateral approach

- Arcuate incision extends from the zygoma on the left, curving superiorly following the coronal suture, transverses the sagittal suture reaching the inferior temporal line on the right.
- Careful attention must be paid to the trajectory of the facial nerve which is below the zygoma!

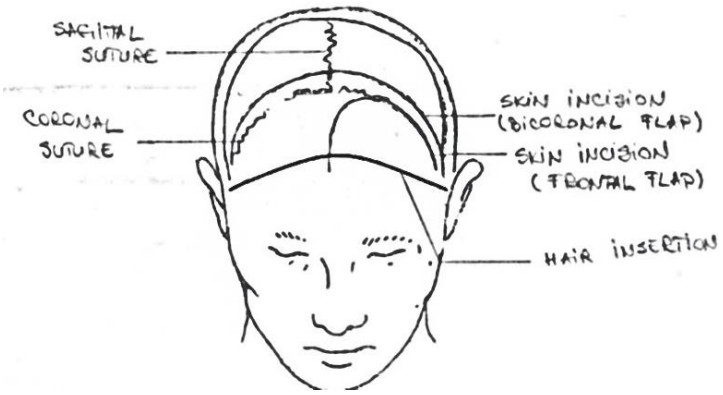

Figure 14. Unilateral and bilateral approach incisions (Illustrations by Andrei Marinescu)

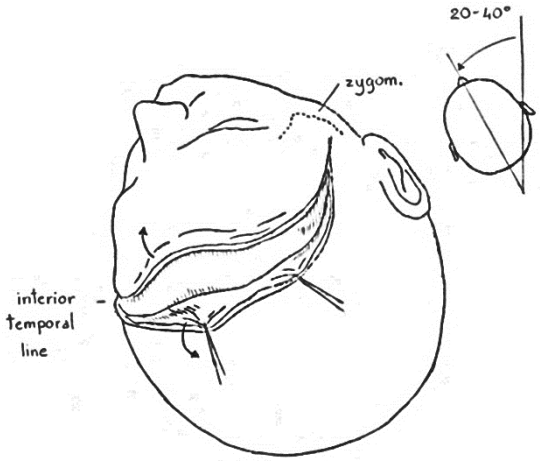

Figure 15. Skin incision for bilateral frontal approach (Illustrations by Andrei Marinescu)

Skin flap

- Incision site infiltrated with 0.5% lidocaine and adrenaline
- The skin is reflected anteriorly on a sponge soaked with saline solution and is covered with a wet gauze. Also, a hook is used to secure it.
- Clips of hemostatic forceps are used for hemostasis.
- The temporal muscle is incised using the electrocautery while sparing the frontoparietal insertion.
- The muscle is reflected laterally and covered with a wet sponge.
- A vascularized portion of the pericranium is harvested for potential use in the repair of dura mater or frontal sinus

Bone flap

- The purpose of the bone flap (Figures 16, 17) is the exposure of the frontal pole and the anterior portion of the Sylvian fissure. 6 burr holes are drilled as follows:

1. Antero-lateral, medial from the insertion of the temporal muscle, carefully not to enter the orbit.

2. Immediately posterior to the pterion

3. 1-2 cm posterior to the coronal suture and above the superior temporal line

4. Immediately posterior to the coronal suture

5. 1.5 cm lateral to the medial line, approximately in the middle between holes 4 and 6

6. As low as possible in the frontal region and 1.5 cm lateral to the medial line to avoid injury to the superior sagittal sinus

- The burr holes are connected with the craniotome in order to avoid injury to the superior sagittal sinus.
- The pterional area requires a drill to remove a part of the lateral sphenoidal wing.
- The bone flap is elevated while stripping the dura

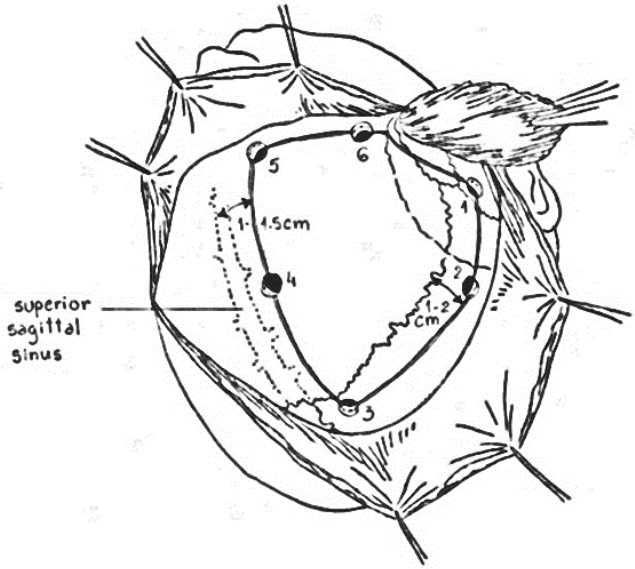

Figure 16. Position of burr holes in unilateral frontal approach (Illustrations by Andrei Marinescu)

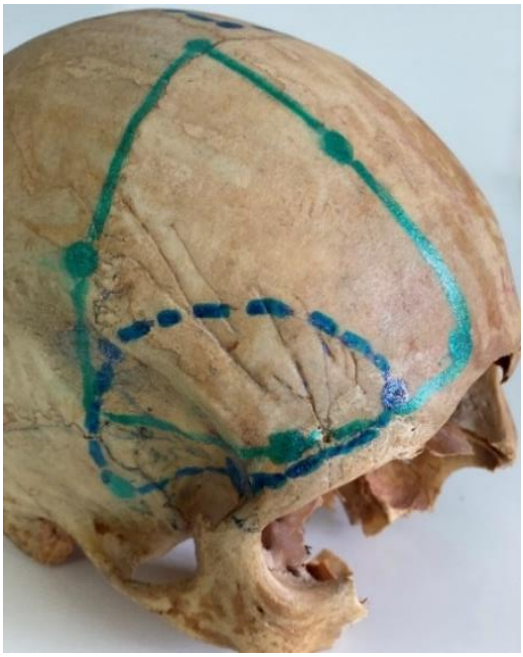

Figure 17. Position of burr holes and their connection made with the craniotome in unilateral frontal approach (green line) (Personal collection of dr. Vicențiu Săceleanu)

Dural opening

- If the dura is still in tension, despite administering Dexamethasone and hyperventilation, 500 ml Mannitol 20% and 20-40 mg Furosemide can be administered
- The dural flap is made in a U-shape with the base following the sagittal sinus at 1.5 cm distance
- In case of a bilateral approach, the sagittal sinus is ligated at its origin to control any unexpected hemorrhage

Closure

- The resection cavity is lined with Surgicel and is irrigated with room-temperature saline solution
- Dura mater is closed watertight using the previously harvested pericranium or muscle if necessary

- Bone flap is replaced and fixed securely with titanium microplates
- Temporalis fascia is approximated with sutures
- Scalp is closed in 2 anatomic layers
- Sterile dressing and head wrap

Complications

- Lesions of the superior sagittal sinus with craniotomy instruments (trephine, craniotome/ Gigli saw)
- Lesions of the superior branches of the facial nerve (CN VII)
- Ineffective hemostasis leading to subdural or epidural hematomas
- Lesions of the anterior cerebral arteries
- Nosocomial infections
- CSF fistula
- Seizures

4. Temporal approach

Anatomy

Delimitations of the temporal region:

- **Superior:** superior temporal line
- **Inferior:** inferior margin of the zygomatic arch
- **Anterior:** the groove formed by the zygomatic process of the frontal bone and the frontal process of the zygomatic bone

Stratigraphy

1. **Skin** – soft, mobile, partially hairy
2. **Subcutaneous layer** – soft connective tissue which contains:
    - the temporoparietal and anterior and superior auricular muscles;
    - their accompanying veins, tributary to the retromandibular vein;
    - branches of the auriculo-temporal nerve;

- lymphatic vessels which travel towards the parotid and mastoid ganglia.

3. **Aponeurotic layer** – the lateral portion of the cranial aponeurosis
4. **Fascial layer** – the temporal fascia inserts on the limits of the temporal region. In the inferior part it splits into a superficial and a deep layer, between which adipose tissue can be found. In case of undernutrition this adipose tissue is absent resulting the specific bony aspect of the skull.
5. **Muscular layer** – consists of the temporal muscle which is contained in an osteo-fibrous fossa. The temporal fossa is contained between the bone layer and the temporal fascia and communicates inferiorly with the infratemporal fossa.

The temporal fossa contains the deep temporal blood vessels and nerves. The arteries are branching from the maxillary artery and the superficial temporal artery. The veins drain into the pterygoid plexus and retromandibular vein. The lymphatic vessels drain into the superficial parotid ganglia and the nerves are branches from the mandibular nerve (CN V_3)

6. **Periosteum**
7. **Bone** – temporal fossa. The outer table of the bone contains the following landmark sutures: the lateral portion of the coronal suture, spheno-frontal suture, squamous suture, and spheno-squamous suture. The endocranial surface presents numerous vascular grooves such as the groove of the middle meningeal artery.

In newborns we find 2 fontanelles: the sphenoid fontanelle (at the junction of the sphenoid, frontal, temporal and parietal bones) and the mastoid fontanelle (at the junction of the occipital, parietal and mastoid bones). Both fontanelles will close shortly after birth.

8. **Dura mater** – very easy to elevate from the temporal bone (Gerard Merchant area), thus facilitating the presence of postoperative epidural temporal hematomas.

Indications

- Biopsy of the temporal lobe (e.g., herpes simplex encephalitis);
- Temporal lobectomy for temporal lobe epileptic areas, posttraumatic craniocerebral decompression or stroke
- Chronic subdural hematoma

Preoperative planning: see general craniotomy techniques

Equipment: see general craniotomy techniques

Anesthesia: see general craniotomy techniques

Positioning:

- supine lateral (45°) or lateral (90°) to allow the head to be in a complete lateral position (parallel to the ground).
- The head is fix in the Mayfield head holder with 2 pins in the occiput and 1 in the frontal region
- The brachial plexus must pe protected: a rolled towel must pe placed under the should!

Antiseptic scrub and surgical field preparation: see general craniotomy techniques

Incision

- A question mark shape incision is made starting above the zygoma, crossing the anterior margin and curves posteriorly reaching 3.5 cm posteriorly to the external acoustic meatus. (Figure 18)
- This way, the branch of the facial nerve that innervates the frontal muscles and the superficial temporal artery are spared.

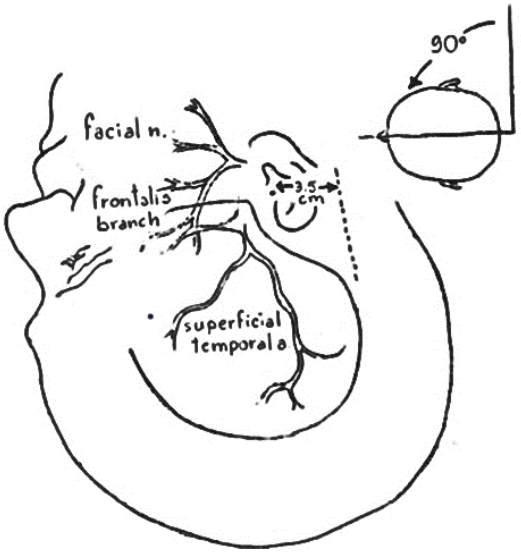

Figure 18. Question mark incision to preserve the superficial temporal artery and the frontal branch of CN VII (Illustrations by Andrei Marinescu)

Skin flap

- The scalp is reflected antero-inferiorly on a wet sponge, is fixed with a hook and covered with a wet gauze (Figures 19, 20)
- The muscle is covered with a wet sponge and is secured with towel clips at its base
- The temporal muscle`s insertion can be spared.

Bone flap

- 5 burr holes are drilled as follows (Figures 21, 22):

1. Antero-inferior, placed just posteriorly to the external contour of the eye and anterior to the pterion in order to expose the temporal pole

2. Posterior-inferior, placed above the zygoma, just at the insertion of the zygomatic arch

3, 4, 5. Posterior and superior in relationship with the scalp.

- The burr holes are connected with the craniotome or the Gigli saw
- The bone flap is elevated
- Wax is used for hemostasis

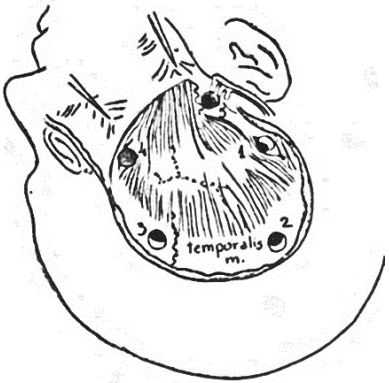

Figure 19. Temporal approach skin and muscle reflected over a wet sponge; position of the 5 burr holes
(Illustrations by Andrei Marinescu)

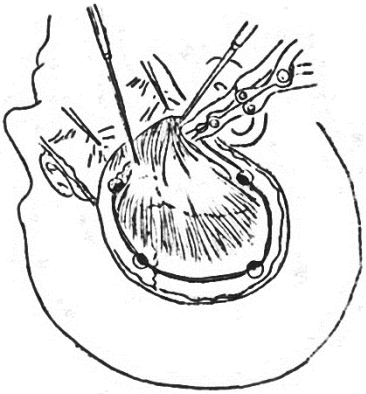

Figure 20. The 5 burr holes are connected with the craniotome
(Illustrations by Andrei Marinescu)

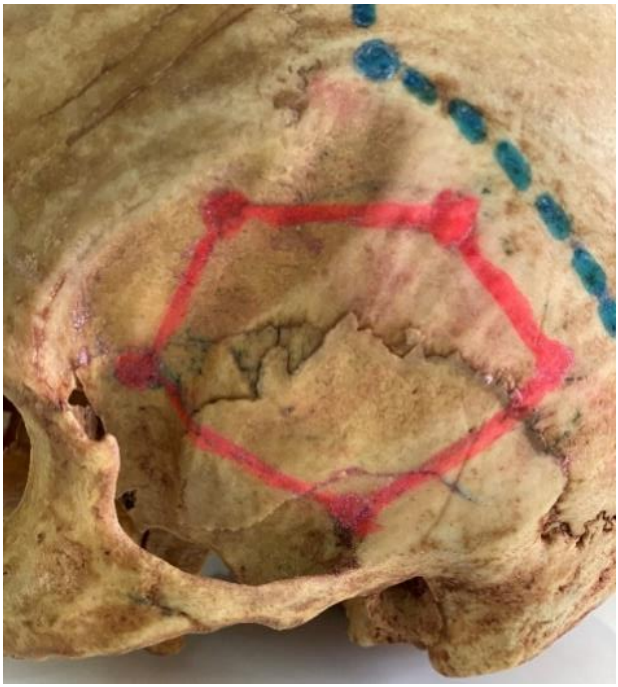

Figure 21. Burr holes and connection as seen on the cranium (Personal collection of dr. Vicențiu Săceleanu)

Dural opening

- Dura is opened in a horseshoe shape, with the base towards the sphenoid bone (Figure 23)
- Bipolar coagulation should be used only if absolutely necessary to avoid shrinkage
- Dura is suspended

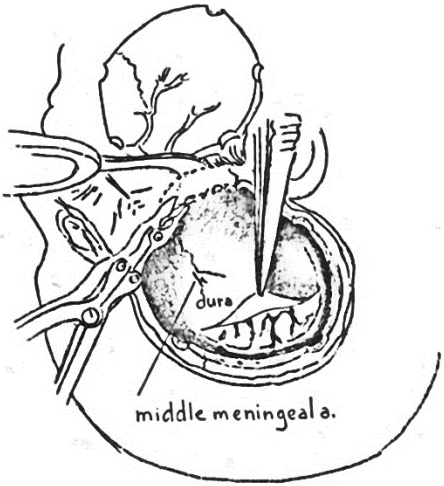

Figure 22. Horseshoe incision of the dura to preserve the middle meningeal artery
(Illustrations by Andrei Marinescu)

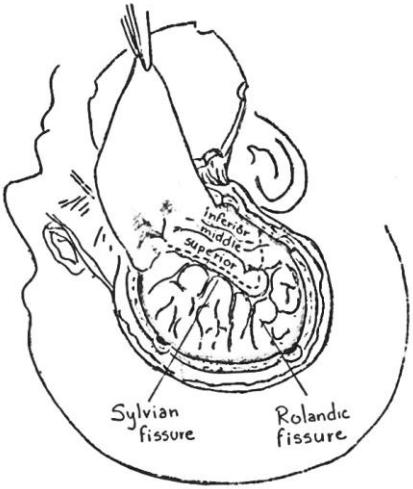

Figure 23. Dura is reflected anteriorly to expose the Sylvian fissure and central sulcus
(Illustrations by Andrei Marinescu)

Closure

- Cavity is well irrigated with room-temperature saline solution and coated with Surgicel
- Cavity is filled with saline solution
- Dura is closed and a central tenting suture is placed
- Small bleeding managed with Gelaspon
- Bone flap is secured with wires or titanium microplates
- Temporalis fascia is approximated with sutures
- Scalp is closed in 2 anatomic layers
- Sterile dressing and head wrap

Complications

- Uncareful positioning of the head can lead to spine injury
- Dural tear
- Lesions of the cerebral tissue due to craniotomy instruments (trephine, craniotome/ Gigli saw)
- CSF fistula: special care should be considered for the mastoid air cells
- Peripheral CN VII palsy
- Aphasia
- Hemiparesis
- Third cranial nerve palsy
- Seizures
- Nosocomial infections

5. Pterional approach

Anatomy

The word "pterion" has its root in the Greek word "pteron", meaning wing. This derives from the Greek god Hermes, the messenger of the gods. He was able to fly thanks to his winged sandals and wings on his head that were inserted on the pterion.

The pterion is located behind the temple, on the lateral side of the cranium. The pterion represents the place where the frontal, temporal, sphenoid, and parietal bones join together. (Figure 24)

Considering the middle meningeal artery is located just below the pterion, a fracture of the pterion is very likely to cause an epidural hematoma.

Stratigraphy: see temporal approach

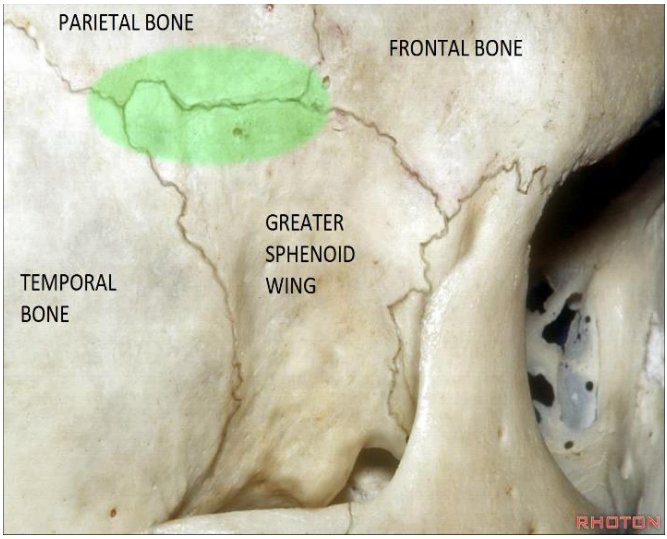

Figure 24. The pterional region highlighted with green (Image source: Rhoton1137-2D by Albert Rhoton; Copyright: Rhoton Collection)

Indications

1. **Aneurysms**
   - All anterior circulation aneurysms
   - Basilary tip aneurysms
   - Sellar, presellar, orbital, subfrontal and optic chiasm aneurysms
2. **Direct approach to the cavernous sinus**
3. **Subfrontal, subtemporal and Sylvian fissure lesions**
4. **Suprasellar tumors**
   - Pituitary adenomas (with a suprasellar component) + sufrontal, subtemporal or optic chiasm

tumors, lesions of the Sylvian fissure

- Craniopharyngiomas

Preoperative planning: see general craniotomy techniques

Equipment: see general craniotomy techniques

Anesthesia: see general craniotomy techniques

Positioning

- Patient is supine with the ipsilateral shoulder slightly raised
- Thorax is raised 10° - 15° to reduce the venous stasis
- Knees slightly flexed
- Neck in slight extension 10° - 15° for gravitational retraction of the frontal lobe
- Head is rotated:
  - 30° - Anterior Inferior Cerebellar Artery (AICA)
  - 45° - middle fossa, AICA aneurysm, Internal Carotid Artery (ICA) aneurysm
  - 60° - anterior part of the Willis Circle: Anterior Communicating Artery, suprasellar aneurysms and tumors
- Head is fixed in Mayfield head holder

Antiseptic scrub and surgical field preparation: see general craniotomy techniques

Incision

- Begins of the median line, curving posteriorly and inferiorly towards 1cm anterior of the tragus, above the zygoma (to spare the superficial temporal artery, frontal branch of the facial artery).
- The interfascial technique offers a better visibility or the "muscle splitting" method offers a musuclo-cutaneous flap (the cutaneous tissue is dissected together with the muscular tissue)
- The muscle and the skin flap is secured with hooks and are protected with wet sponges & gauze
- If the interfascial dissection is preferred, the skin is retracted together with the adipose tissue to not harm the facial nerve

Bone flap

- 1 to 5 burr holes can be used for this approach, depending on the surgeon`s preference; we recommend minimum 3:
  1. Keyhole: under the superior temporal line at its anterior extension, just over the fronto-zygomatic suture
  2. In the frontal bone, 3-4 cm from the first burr hole, near the superior orbital margin, avoiding entering the frontal sinus
  3. Posterior, under the superior temporal line, immediately anterior of the coronal suture (Figure 25)

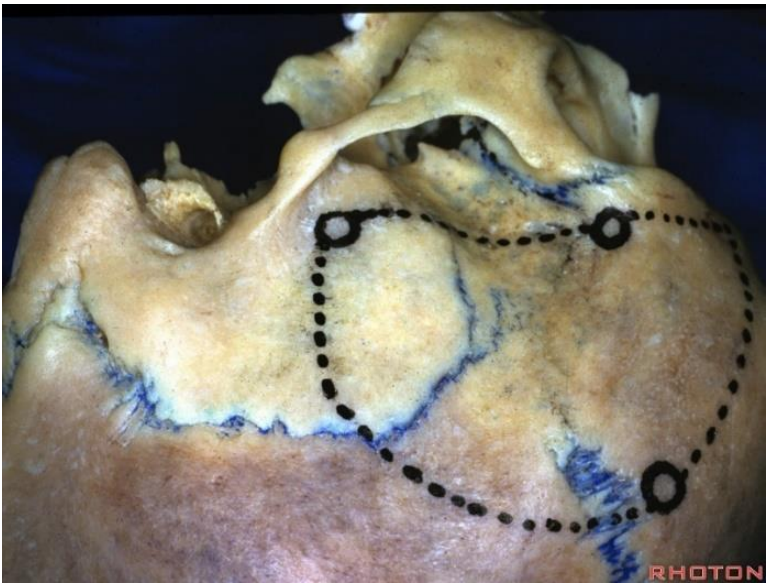

Figure 25. Burr holes and connection with craniotome in pterional approach
(Image source: Rhoton0125-2D by Albert Rhoton; Copyright: Rhoton Collection)

- The burr holes are connected with the craniotome
- The sphenoid wing is extensively drilled until the medial margin of the small sphenoid wing is reached, which is

usually marked by the orbital meningeal artery

- The more the bone resection is directed inferiorly, the better the temporal lobe is exposed and will require little to ne retraction
- Small holes are drilled at the bone edges for dura mater suspension and better securing of the bone flap at closure
- Dura mater is elevated from the sphenoid wing and the bone is resected leaving in place only a thin portion of the superior and lateral margins, posterior of the orbit
- The meningo-orbital artery is coagulated
- For the proximal carotid aneurysm, the thin posterior orbital wall is resected, exposing the periorbita, continuing the medial advance until the optic nerve can be seen
- The remaining clinoid processes are resected, thus any change in the aneurysm`s status can be observed

Dural opening

- Dura mater is incised in a semicircle, above the sylvian fissure with an inferior or anterior-inferior pedicle
- Dura mater is suspended so as not to obstruct the view
- If the brain is not well decompressed, the frontal lobe is slightly retracted to drain CSF from the basal cisterns
- The most important aspect is the arachnoid dissection starting from its free part situated in the Sylvian fissure
- With a scalpel the fronto-temporal arachnoid adherences are separated, beginning 2-3 cm posterior of the sphenoid wing, on the frontal lobe side
- The dissection continues medially until M2 branches of the middle cerebral artery (MCA) emerge
- The M2 branches are followed until the corpus callus genus is seen, then the fissure is carefully opened by separating the fronto-temporal adhesions
- The basal cisterns that surround the internal carotid artery and the optic nerve are opened, contributing to cerebral relaxation
- Using autostatic retractors, the frontal and temporal

lobes are separated

- Special care should be paid in sparing the sphenoparietal vein

Closure

- The cavity is well irrigated with room-temperature saline solution and coated with Surgicel
- Dura mater is closed with 4.0 silk
- If dura is still bleeding slightly, Surgicel is placed on the hemorrhagic spot
- The harvested pericranium is used for patching dura mater defects if necessary
- Dura is tented on the center of the bone flap
- Bone flap is secured in place with titanium microplates
- Muscle is reapproximated with sutures
- Scalp is closed in 2 anatomic layers
- Sterile dressing and head wrap

Complications

- The main intraoperative complications involve the penetration of the frontal sinus or the orbit when creating the bone flap
- Those situations can be repaired by waxing the defect and/or by using the harvested pericranium to cover it
- If frontal sinus is penetrated a CSF fistula is very likely to occur
- Seizures
- Nosocomial infections

6. Occipital approach

Anatomy

Limits of the region:

- **Posterior** – external protuberance and superior nuchal lines which divide it from the nuchal region
- **Lateral –** base of the mastoid process which divide it from the sternocleidomastoid region
- **Anterior –** continues with the parietal region

- **Medial –** continues with the other occipital region

Stratigraphy

- **Thick skin**
- **Subcutaneous layer –** very little fat tissue, rich in connective fibers with binds the skin to the epicranian aponeurosis
- **Muscles and aponeurosis** – epicranial aponeurosis with the occipital muscle which inserts on it

Those 3 layers form the scalp.

The subcutaneous layer contains vascular and nervous elements: branches of the occipital artery, posterior auricular artery (branch of the external carotid artery). The veins follow the arteries closely, resulting in a network of vessels traveling towards:

- the diploic vessels or
- emissary vessels of the dural sinuses
- exocranial vessels

The lymphatic vessels drain towards the occipital ganglia. The nerves are represented by C2 and C3 occipital nerves.

- **Subaponeurotic layer** – soft connective tissue offering mobility
- **Periosteum** – adherent to the cranial sutures
- **Bone** – posterior fontanelle between parietal and occipital bones closes 1 year after birth. This fontanelle is important for the early diagnosis in rickets
- **Dura mater** – the superior sagittal sinus is present on the midline. At this level, the superior sagittal sinus forms the torcular Herophilus (sinus confluence)

Indications

- Occipital lobe tumors, including falx meningioma or tentorial meningioma
- Occipital intraparenchymal hemorrhage
- Occipital lobe trauma
- Angiomas, infratentorial tumors, pineal gland approach

Preoperative planning: see general craniotomy techniques

Equipment: see general craniotomy techniques

Anesthesia: see general craniotomy techniques

Positioning

- Prone position, special care is paid not to compress the jugular veins
- Head can be in slight flexion and ¾ rotation
- 3-pin Mayfield head holder

Antiseptic scrub and surgical field preparation: see general craniotomy techniques

Incision

- Skin incision begins on the midline at the superior nuchal line and goes anterior following the midline, then curves lateral and caudal in order to end just lower than the squamous suture
- Skin flap reflected caudally to avoid injuring the occipital artery and the smaller and greater occipital nerves (Figure 26)

Bone flap

- 3 burr holes are made and connected with the craniotome or manually with the Gigli saw
  1. Postero-superior temporal region
  2. 1 cm from the margin of the superior sagittal sinus
  3. In the occipital region, 1 cm above the transverse sinus and 1 cm lateral to the superior sagittal sinus

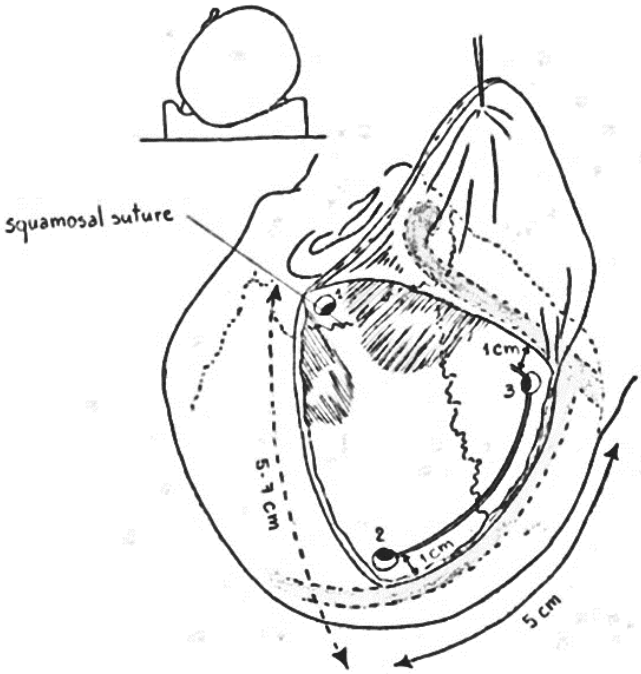

Figure 26. Patient prone position, head ¾ rotation, skin flap is reflected caudally, 3 burr holes are placed and connected with the craniotome or Gigli saw
(Illustrations by Andrei Marinescu)

Dural opening

- Dura mater is suspended (Figure 27)
- Incision is made in "T" shape to reflect the dura both on the superior sagittal sinus and on the transverse sinus

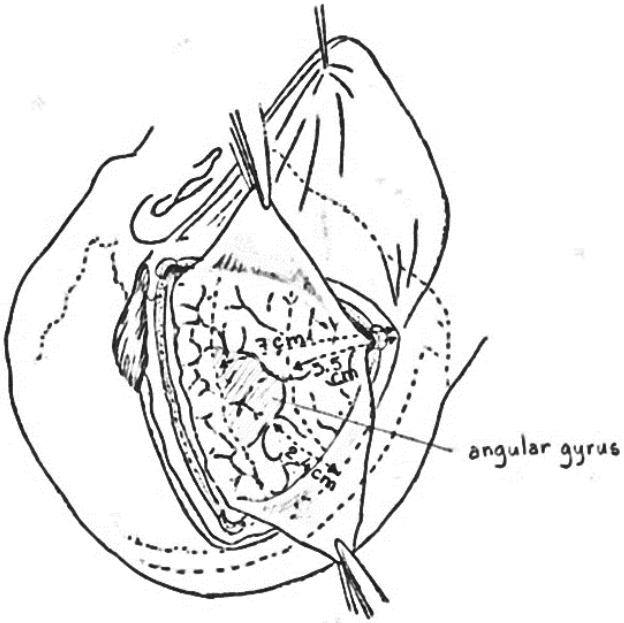

Figure 27. Dura mater is opened in "T" shape, reflecting one side on the superior sagittal sinus and the other on the transverse sinus. Angular gyrus is exposed.
(Illustrations by Andrei Marinescu)

Closure

- The cavity is well irrigated with room-temperature saline solution and coated with Surgicel
- Dura mater is closed watertight with 4.0 silk
- If dura is still bleeding slightly, Surgicel is placed on the hemorrhagic spot
- The harvested pericranium is used for patching dura mater defects if necessary
- Dura is tented on the center of the bone flap
- Bone flap is secured in place with titanium microplates
- Muscle is reapproximated with sutures
- Scalp is closed in 2 anatomic layers

- Sterile dressing and head wrap

Complications

- Lesions of the superior sagittal sinus or transverse sinus with craniotomy instruments
- Lesions of the C1 and C2 occipital nerves
- Lesions to the occipital lobe visual cortex resulting in new visual field deficit
- Poor hemostasis resulting in subdural or epidural hematoma
- Seizures
- Nosocomial infections

7. Median and paramedian suboccipital approach

Anatomy: see occipital approach

Stratigraphy: see occipital approach

Indications

- Median and paramedian posterior cranial fossa lesions
  - Vermian and paravemian lesions (vermian astrocytomas, arteriovenous malformations)
  - 4^{th} ventricle tumors (ependimomas, medulloblastomas)
  - Pineal gland lesions
  - Expansive processes in the brain stem
  - Skull base lesions
  - Cerebellar lesions (metastases, hemangioblastomas, hematomas) that are smaller than 2.5 cm in diameter
- Quick treatment of obstructive hydrocephalus
- Decompressive craniectomy in case of
  - Arnold-Chiari malformation
  - Cerebral/cerebellar infarction
- Pontocerebellar angle lesions
  - Vestibular schwannomas
  - Pontocerebellar angle meningiomas
  - Epidermoid tumors

- Microvascular decompression for
  - trigeminal neuralgia
  - hemifacial spasm
  - corpus callosum genu or glossopharyngeal neuralgias

Preoperative planning: see general craniotomy techniques

Equipment: see general craniotomy techniques

Anesthesia: see general craniotomy techniques

Positioning

- Patient in prone, sitting, or lateral recumbent position
- In general, prone position is preferred except for obese patients
- Head is fixed in 3-pin Mayfield head holder
- Best head stability is obtained if the 2 most anterior pins are placed on the superior temporal line behind the hairline; pin fixation on the squamous part of the temporal bone must be avoided
- The horizontal bar of the Mayfield head holder must be rotated above the nasion for optimal positioning
- Skin pressure points are padded with towels
- Shoulders are aligned to the edge of the operating table

Antiseptic scrub and surgical field preparation: see general craniotomy techniques

Incision

- Skin incision begins on the medial line from the spinous process of the C2 vertebra towards the head at 2 cm above the external occipital protuberance
- Dissection of anatomic layers until the cervical fascia is reached to limit hemorrhaging
- Paraspinal muscles are elevated from C1 vertebra lamina with electrocautery
- Lateral subperiostal dissection
- Occipital bone muscles are elevated lateral of the superior nuchal line

- Extension of the dissection layers in cranio-caudal direction will be realized depending on the lesion location with or without craniectomy in the foramen magnum region

Bone flap (Figure 28)

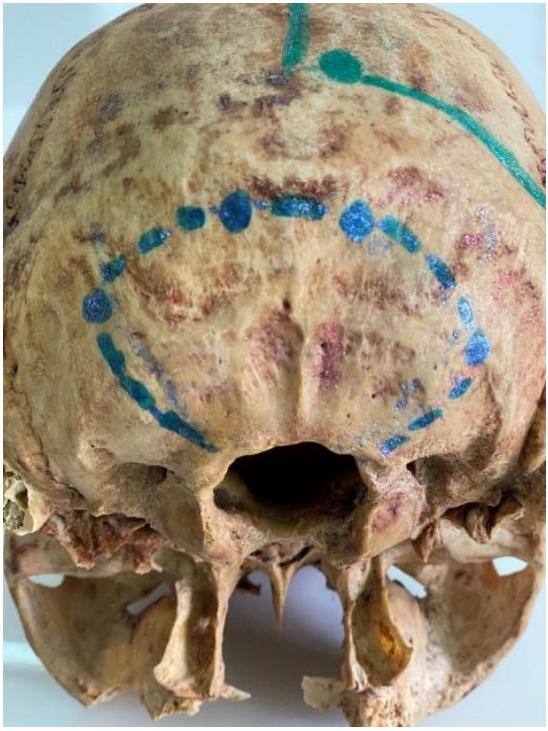

Figure 28. The craniectomy area consists of the space between the projection of the superior venous sinuses, laterally the projection of both cerebellar lobes and inferiorly depending on the extension of the lesion (Personal collection of dr. Vicențiu Săceleanu)

Dural opening (Figure 29)

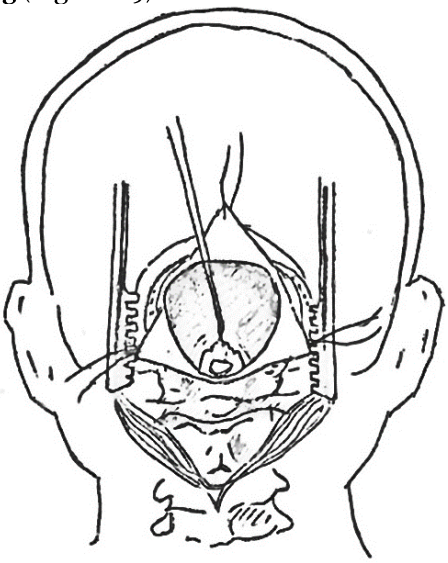

Figure 29. Dura mater is suspended, incision is made in "Y" shape with the superior pedicle reflected over the venous sinus. Cerebellum can be gently retracted for a better observation of the lesion.
(Illustrations by Andrei Marinescu)

Closure

- The cavity is well irrigated with room-temperature saline solution and coated with Surgicel
- Dura mater is closed watertight with 4.0 silk
- If dura is still bleeding slightly, Surgicel is placed on the hemorrhagic spot
- The harvested pericranium is used for patching dura mater defects if necessary
- Dura is tented on the center of the bone flap
- Bone flap is secured in place with titanium microplates
- Muscle is reapproximated with sutures
- Scalp is closed in 2 anatomic layers
- Sterile dressing and head wrap

Complications

- Lesions of the venous sinuses – can be avoided through a careful incision of dura mater; superior pedicle is reflected over the venous sinus
- If elevated intracranial pressure, cerebellar herniation is possible – can be prevented with administration of mannitol and hyperventilation and opening and draining of cerebrospinal fluid from cisterna magna
- If gaseous embolism is suspected:
    - Abundant irrigation with saline solution of the craniotomy area and lowering of the head below the heart.
    - If patient hemodynamically unstable and unresponsive to the above maneuvers, Mayfield head holder is removed, and patient is positioned in reverse left Trendelenburg position.
    - Direct aspiration of gaseous embolism through central line
- Pseudomeningocele – can be prevented with tight suturing of cervical fascia and suturing of galea over the occipital protuberance
- Epidural or subdural hematoma
- Cranial nerves lesion
- Cardiac arrythmia due to manipulation of 4th ventricle floor
- CSF fistula
- Nosocomial infection

8. Trauma flap: decompressive hemicraniectomy

Indications

Decompressive hemicraniectomy is indicated in reducing the elevated intracranial pressure and prevent cerebral herniation in cases such as:

- acute subdural hematoma
- cranial gunshot wound

- intracerebral hematomas
- malignant middle cerebral artery infarct
- ruptured AVM with cerebral swelling
- poor grade subarachnoid hemorrhage
- subdural empyema
- intractable intracranial hypertension

Decompressive hemicraniectomy is a procedure indicated in life threatening situations.

Preoperative planning

Review imaging (CT scans) and note: location and size of lesion, midline shift, other cranial pathology, hydrocephalus. Coagulation status must be checked. In case of trauma, care should be taken to cervical spine. If surgical decompression is indicated, it should be performed as soon as possible.

Equipment detailed in general craniotomy techniques plus:

- ventricular drain in case of hydrocephalus
- aneurysm clips in case of ruptured aneurysm

Anesthesia detailed in general craniotomy techniques plus:

- Normotension should be maintained
- Transfusion products must be available.

Positioning

- The patient is positioned supine, and head turned sideways towards the contra lateral side. It is important to avoid compressing the jugular veins, which can further elevate intracranial pressure.
- Rigid head holder is used only if any skull fractures have been excluded.

Sterile scrub and prep: see general craniotomy techniques

Incision (Figures 30, 31)

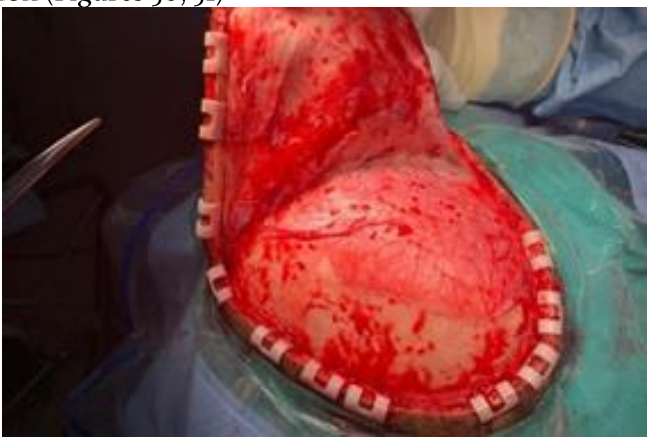

Figure 30. Scalp incision is large and made in question mark. It starts at the zygoma, then bends around the ear towards posterior and returns lateral to the sagittal suture for finishing at hairline.
(Personal collection of dr. Vicențiu Săceleanu)

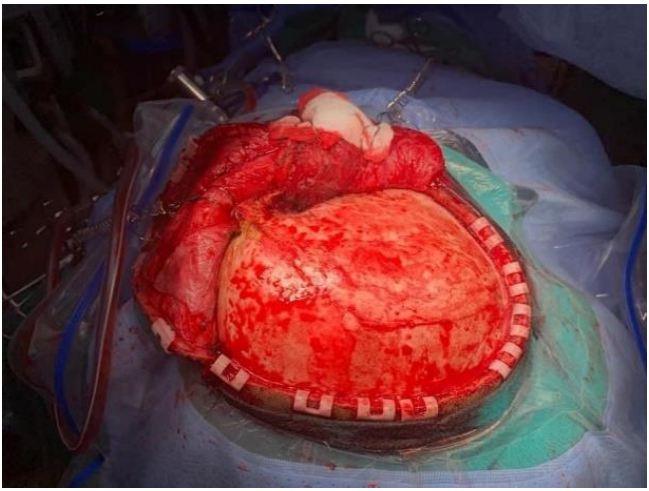

Figure 31. The incision is carried through temporalis fascia and muscle. These can be reflected anterior and fixed with hooks, to ensure sufficient bone window exposure.
(Personal collection of dr. Vicențiu Săceleanu)

Craniotomy

- Three or more burr holes are made: one in temporal squamosa, one in posterior extent and one in frontal near midline. (Figures 32-35)
- The bone flap must be at least 10 x 15cm.
- Bone flap must offer exposure to:
    - inferior – middle fossa floor,
    - posterior – 2 cm of transverse sinus,
    - superior – 1.5cm of the of the midline,
    - anterior – anterior fossa floor.

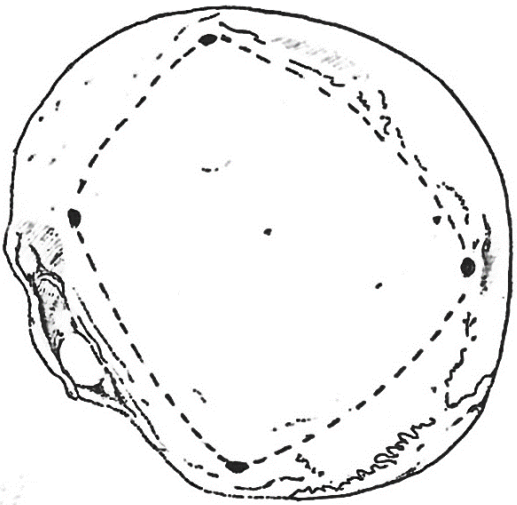

Figure 32. Trauma flap burr hole positions (Illustrations by Andrei Marinescu)

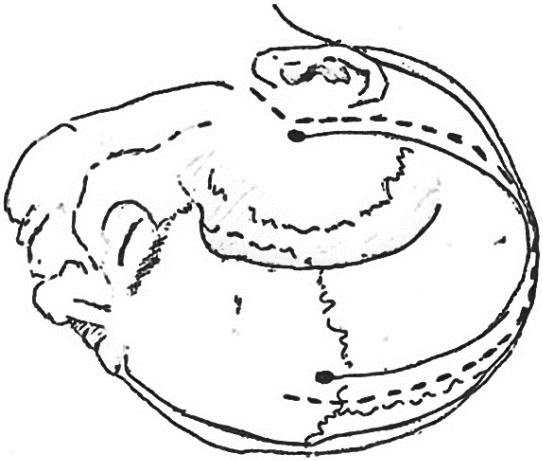

Figure 33. Trauma flap - burr holes connected with craniotome (Illustrations by Andrei Marinescu)

Figure 34 A. Burr hole positions are measured with a sterile ruler (Personal collection of dr. Vicențiu Săceleanu)

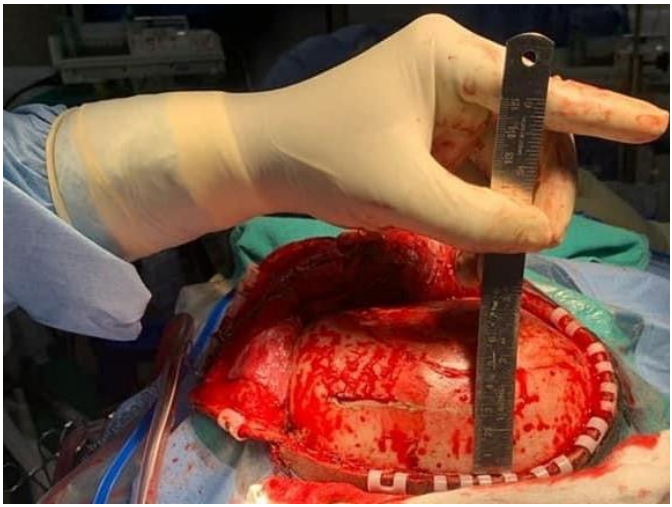

Figure 34 B. Burr hole positions are measured with a sterile ruler (Personal collection of dr. Vicențiu Săceleanu)

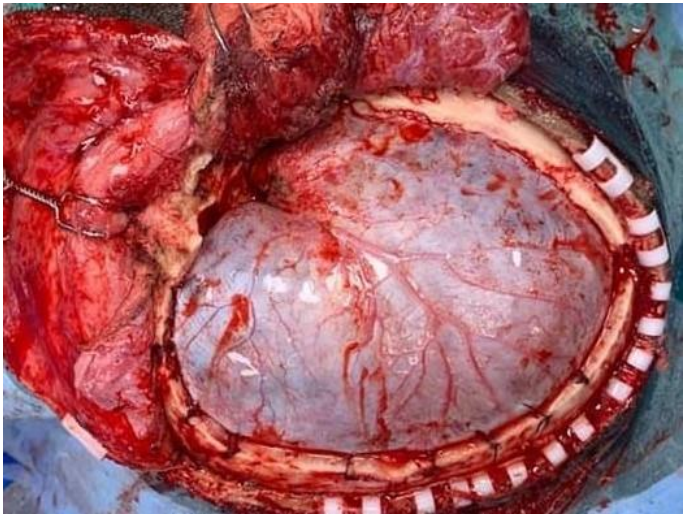

Figure 35. After the bone flap is elevated, wax is used on bone edges for bleeding control and to minimize risk of air embolism. (Personal collection of dr. Vicențiu Săceleanu)

Dural Opening

- Dural opening can be performed by a cruciate incision or by a C-shaped anterior curved incision. In case of associated hematoma, it can be evacuated by suction and irrigation.

Closure

- Duroplasty or simple cover with dural substitute material can be used for closure.
- A subgaleal drain is placed over and tunneled externally.
- The galea is closed with multiple closely spaced 2-0 sutures (Vicryl).
- The scalp is closed with 4-0 monofilament sutures.
- Sterile head bandage is applied.

Postoperative care

Patient will be kept sedated and intubated in the ICU, with continuous monitoring of ICP and BP. The drain can be removed after 24 hours. Anticonvulsant medication should be given for 7 days.

Complications

A. Intra-operative:

- Sinus damage with subsequent intractable hemorrhage,
- Brain edema

B. Postoperative:

- Hematoma,
- Hygroma,
- New infarction,
- Nosocomial infection

Disclaimer: The authors have no conflict of interests to declare.

Abbreviations: AICA - Anterior Inferior Cerebellar Artery, **AVM** – arteriovenous malformation, **MCA** – middle cerebral artery, **CN** – cranial nerve, **CSF** – cerebrospinal fluid, **CUSA –** Cavitron Ultrasonic Surgical Aspirator, **BP** – blood pressure, **CT** – computer tomography, **EEG** – electroencephalogram, **EMG** – electromyogram, **ICP** –

intracranial pressure, **ICU** – intensive care unit, **MRI** – magnetic resonance imaging.

Disclaimer: *The authors have no conflicts of interest to declare.*

References:

1. Rahul Jandial, Paul McCormick, Peter Black, Core Techniques in Operative Neurosurgery, 2011.
2. E.Sander Connolly, Guy M. McKhann, Judy Huang, Tanvir F. Choudhri, Ricardo J. Komotar, J Mocco, Fundamentals of Operative Techniques in Neurosurgery, Thieme, second edition, 2010
3. Alfredo Quiñones-Hinojosa, Schmidek & Sweet Operative Neurosurgical Techniques, sixth edition, Saunders, 2012
4. Mark S. Greenberg. Handbook of Neurosurgery, ninth edition, Thieme, 2019

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