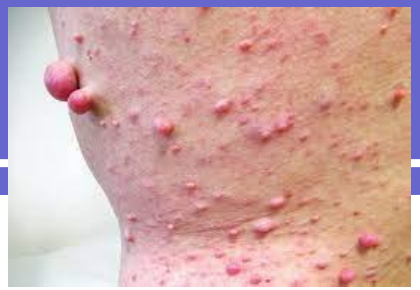
Brain tumors

Epidemiology

- The annual global age-standardized incidence of primary malignant brain tumors is
- ~ 3.7 per 100,000 in men and
- ~ 2.6 per 100,000 in women

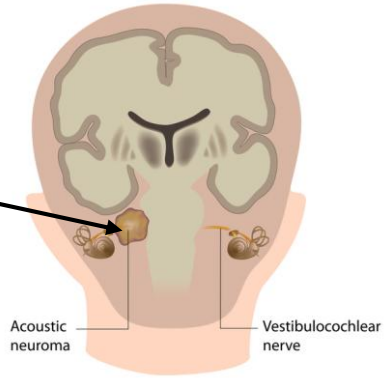
- The global age-standardized mortality rate from primary malignant brain tumors is
- ~ 2.8 in men and
- ~ 2.0 in women per 100,000

Etiology

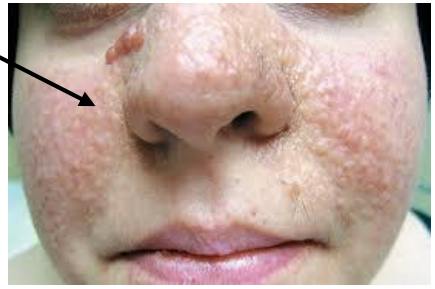


- Genetic factors - Neurofibromatosis - typ 2 historically called von Recklinghausen's disease,

  Tuberous sclerosis - mutation TSC1 or TSC2 gene (chromosome 6 and 9)



- Viral infections: Epstein-Barr virus infection has been associated with primary CNS lymphoma

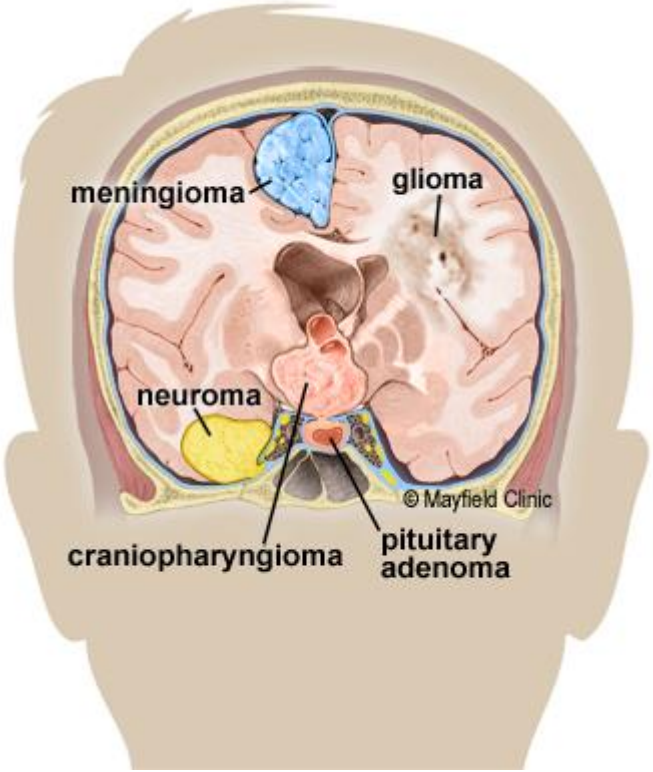


- Environmental factors: pesticides, chemicals, condition after radiotherapy

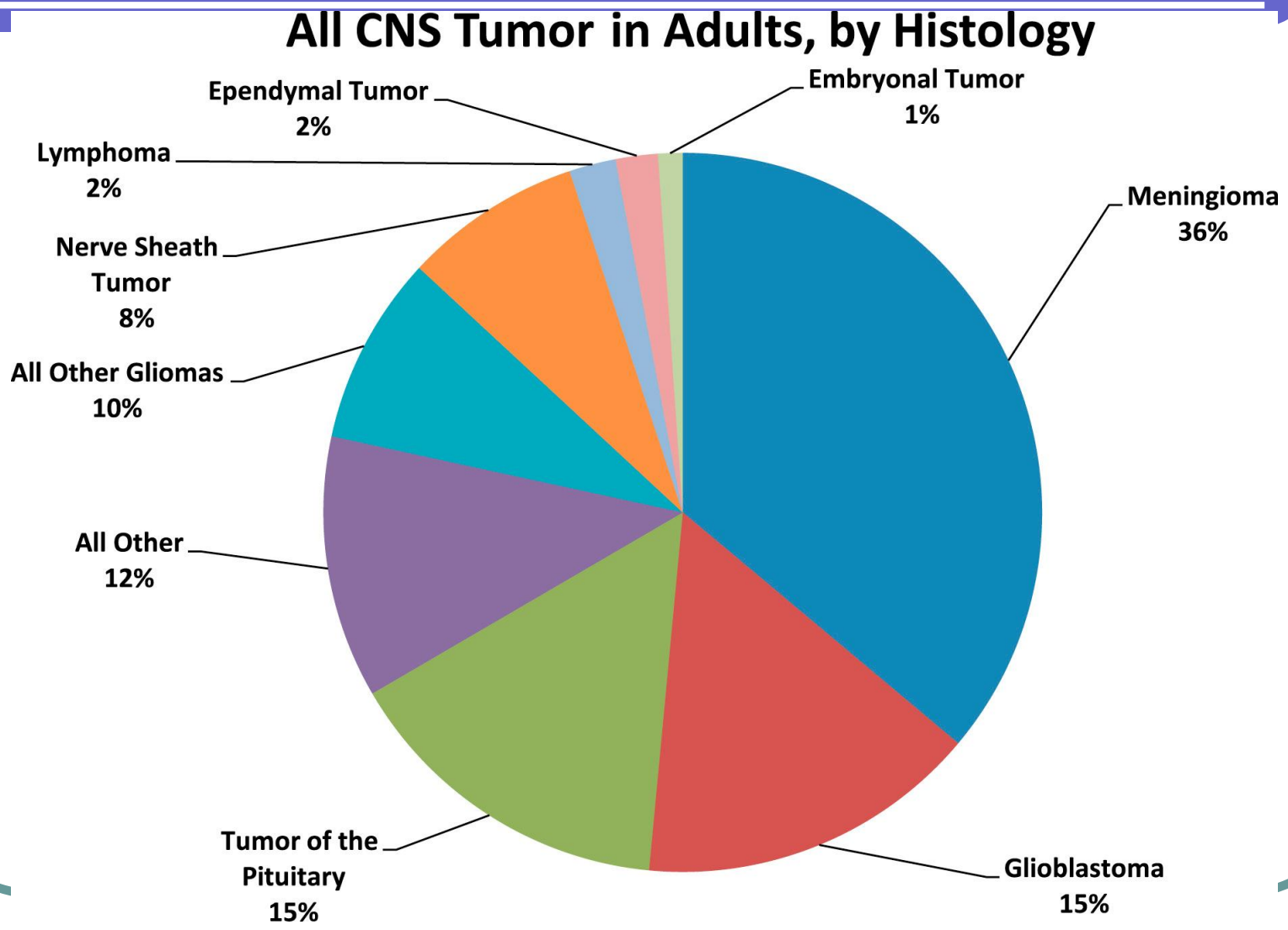
The origin of brain tumors

- Brain tumors can grow

- from nerves (neurinomas),
- from the dura mater (meningioma)
- from the pituitary gland (craniopharyngioma or pituitary adenoma).
- from the brain tissue itself (glioma).

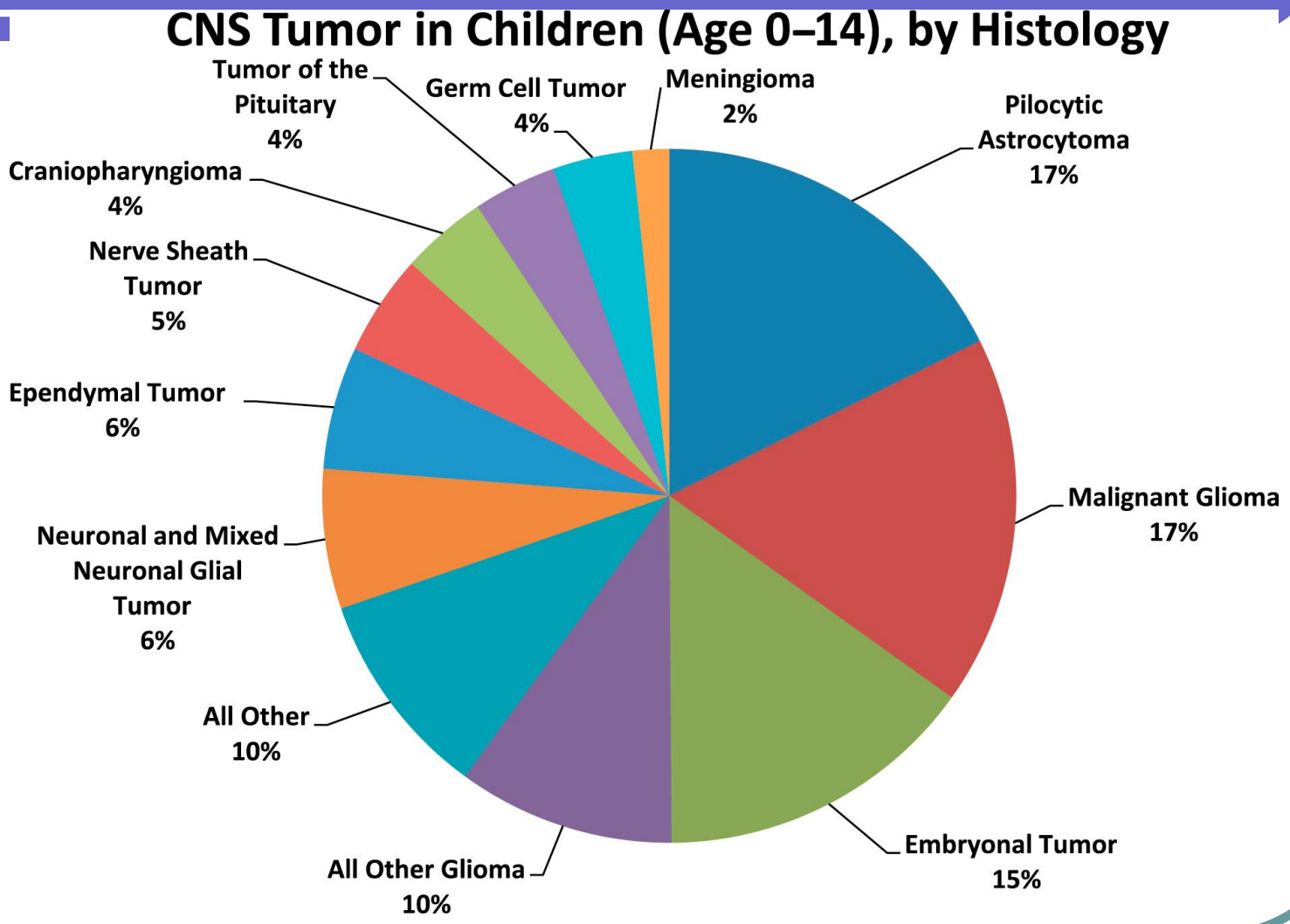


Brain tumors in adulthood



Ostrom QT et al. Neuro Oncol 2014;16 Suppl 4:iv1–iv63

Brain tumors in childhood



Ostrom QT et al. Neuro Oncol 2014;16 Suppl 4:iv1–iv63

Brain tumors classification

Neuroepitelial tumors

1. Astrocytic tumors

   Astrocytoma

   I, II benign

   - III (anaplastic astrocytoma) / malignant je malígny
   - IV (gliobastoma multiforme)

2. Oligodendroglial tumors

   Oligodendroglioma

3. Ependymal tumors

   Ependymoma

Brain tumors classification

4. Mixed gliomas
5. Neuroepitelial tumors – unknown etiology
6. Chorioidal plexus tumors

   Papiloma, papilocarcinoma

7. Neuronal and mixed neuronalglial tumors
8. Pineal parenchymal tumors
9. Tumors with neuroblastic or glioblastic elements (embryonal tumors)

   Meduloblastoma

Brain tumors classification

Other CNS tumors

1. Tumors of sellar region
    1. Pituitar adenoma
    2. Pituitar karcinoma
    3. Kraniofaryngeoma
2. Hemopoetic tumors
    1. Primary malignant lymfoma
    2. Plazmocytoma

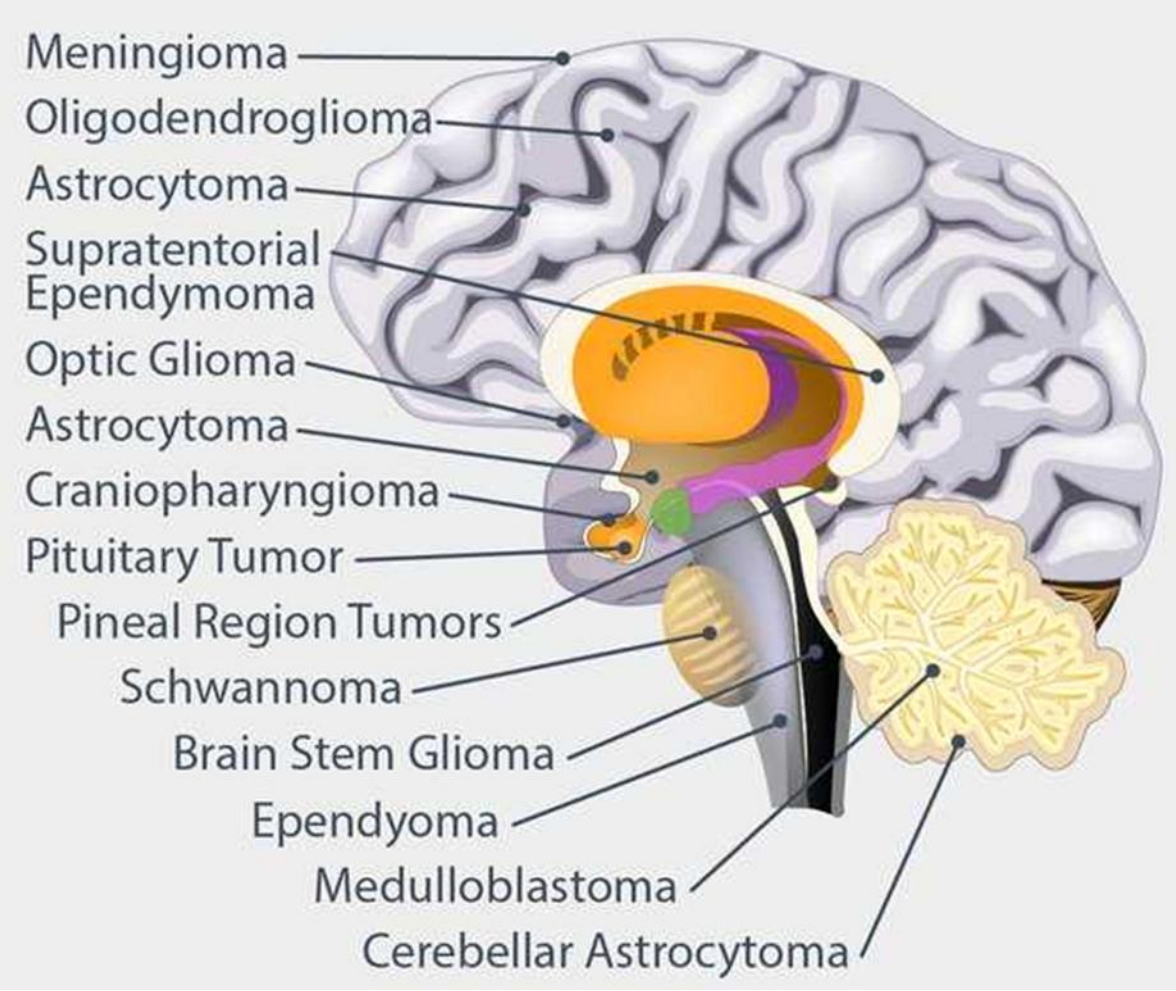
Brain tumors classification

3. Tumors from germinativ cells
4. Meningioma
5. Non-meningotelial meningeal tumors
   - malignant melanoma
   - malignant lymphoma

Brain tumors classification

6. Tumors of cranial and spinal cord nerves
   - Neurinoma (Schwannoma)
   - Neurofibroma
7. Local tumors
   - Chondrosarkoma
   - Chondrocarcinoma
8. Metastatic tumors
9. Nonclassified tumors
10. Cysts

Brain tumors



Secondary tumors

- 25% of all tumors
- In 75% - multiplices
- Not only brain tissue but also meninges can be affected – meningeal carcinomatosis (malignant cells are in CSF)

Secondary tumors

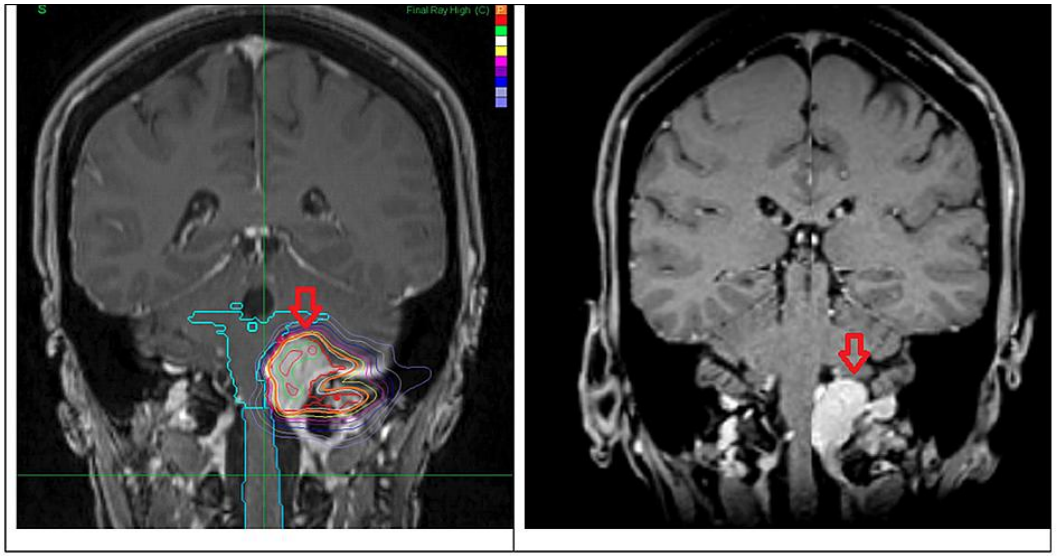
Originate from malignant tumors located primarily in other organs

- Lung
- Breast – breast carcinoma
- Skin - Malignant melanoma
- Kidney - hypernephroma
- Colon – colon carcinoma

These tumors cells reach the brain via the blood-stream

Benign versus malignant?

- Malignant
- 1/ histology (cell atypia, massive mitotic activity, abnormal mitoses)
- 2/ localisation



CyberKnife radiosurgery

Clinical feature

1. General symptoms

- Epileptic seizure

  Focal, generalized

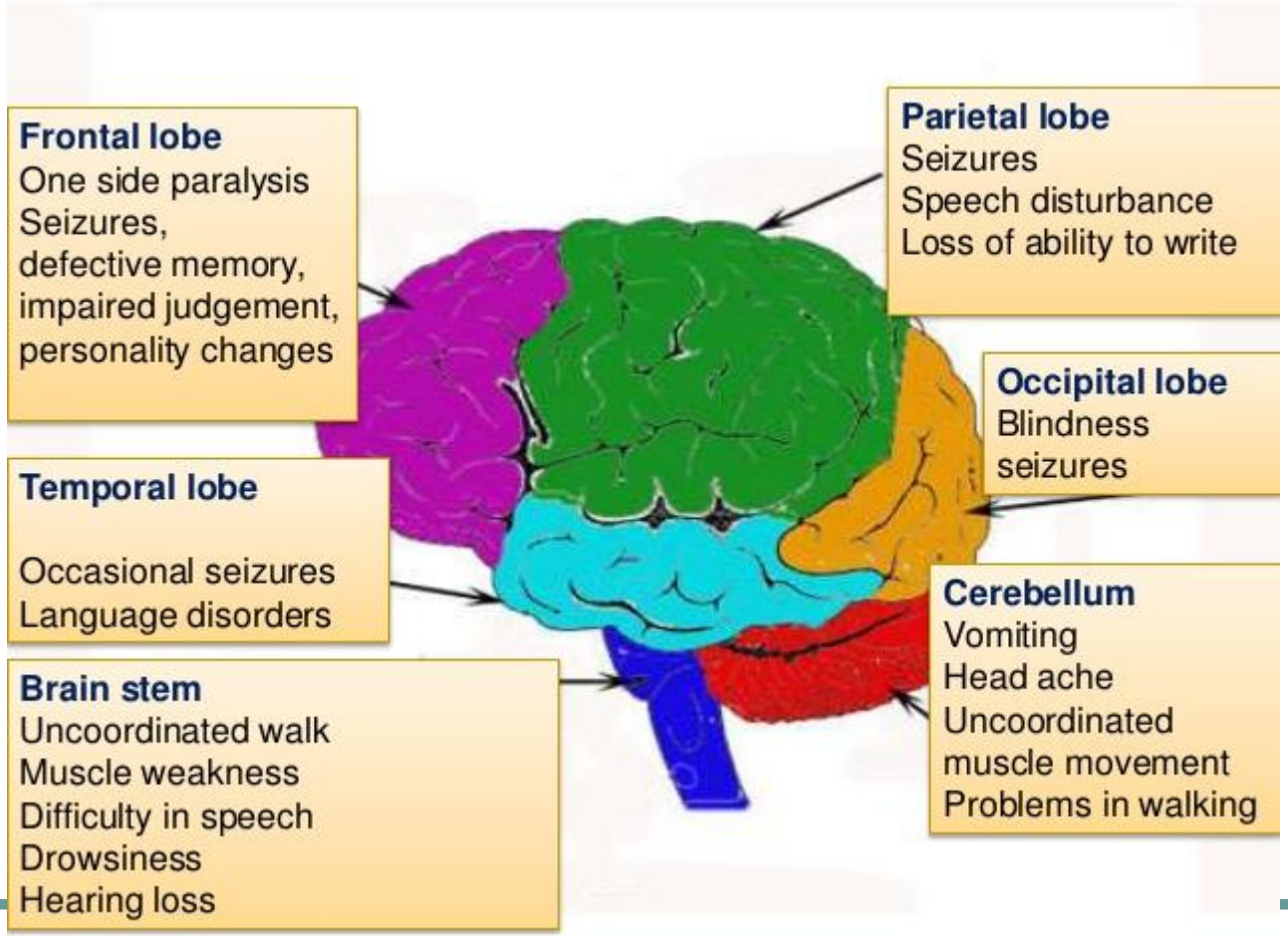
- Intracranial hypertension syndrome
  - Headache, nausea, vomiting (projectile in children), dizziness, blurred vision
  - Papilledema - optic disc swelling
- Psychological changes - behavioral disorders

Clinical feature

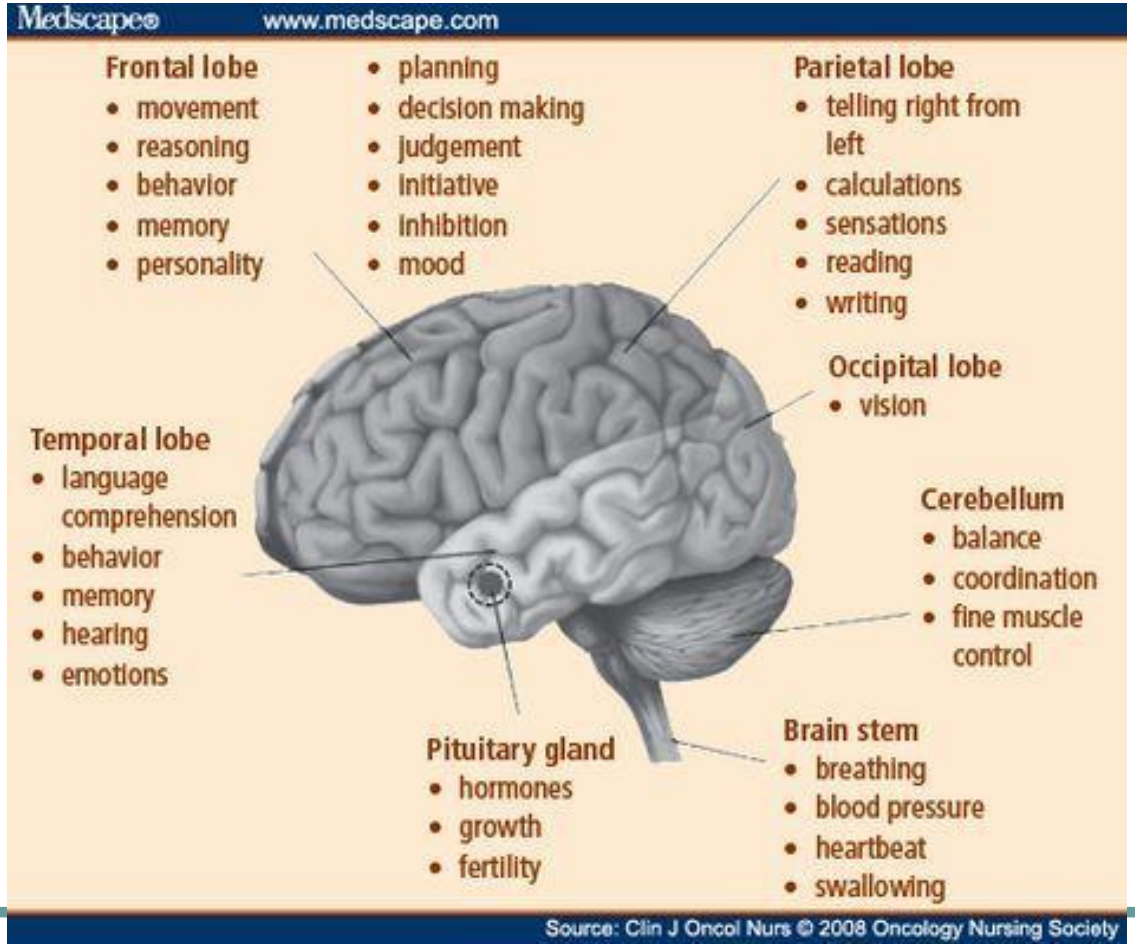
2. Focal symptoms

- It depends on the location of the tumor
- Motor, sensory, sensitive problems, psychological changes, gnostic problems

Clinical feature



Clinical feature

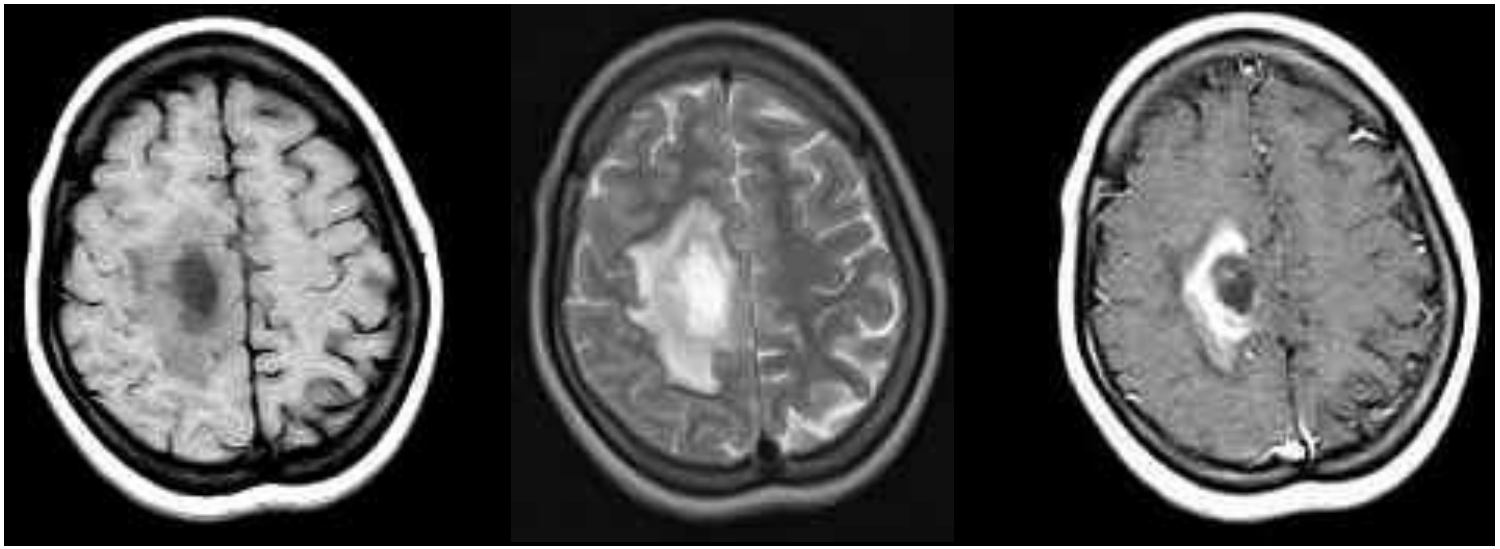


I. Neuroepitelial tumors

- **Astrocytic tumors**

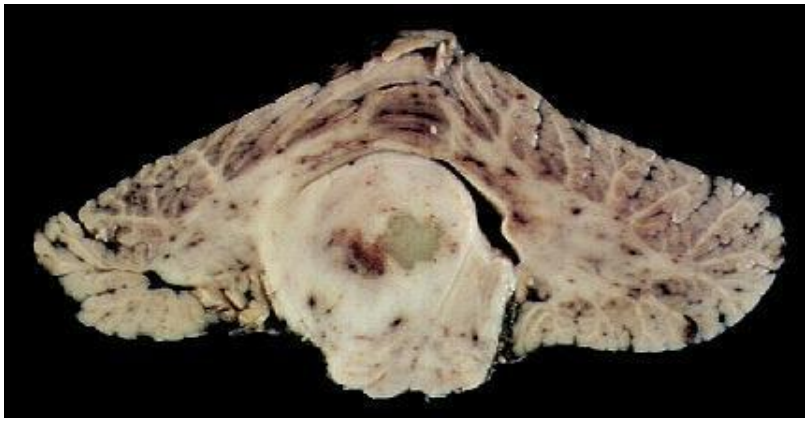
  4 grades of malignity
  - I, II benign
  - III (anaplastic astrocytoma) – malignant
  - IV (gliobastoma multiforme)
- Adults
- Frontal and temporal lobe
- Rarely in childhood – pons

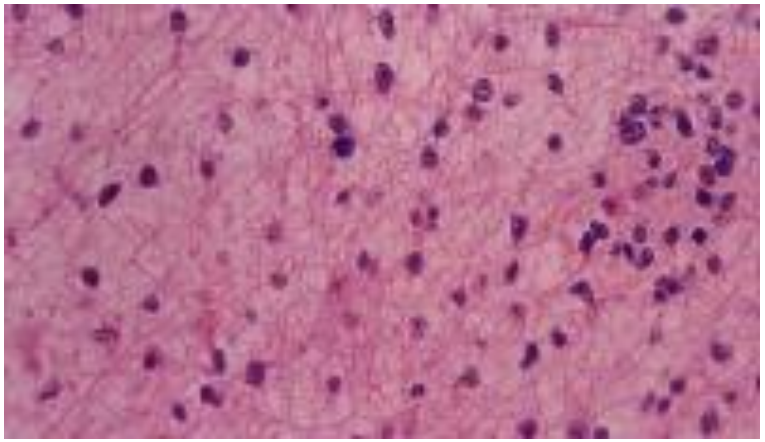
Astrocytoma



MRI T1 weighted T2 weighted flair

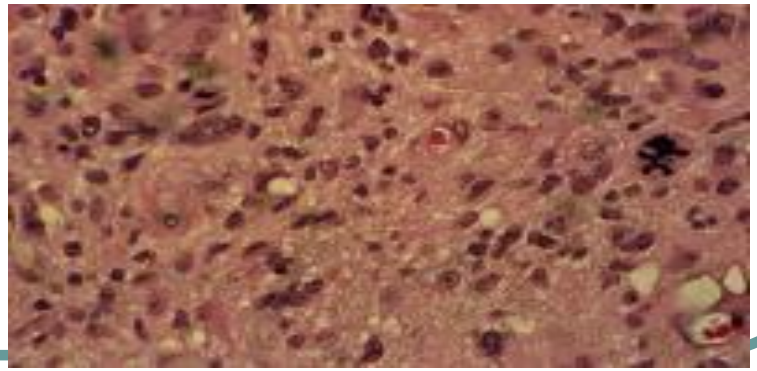
Astrocytoma





Astrocytoma – low grade – in pons

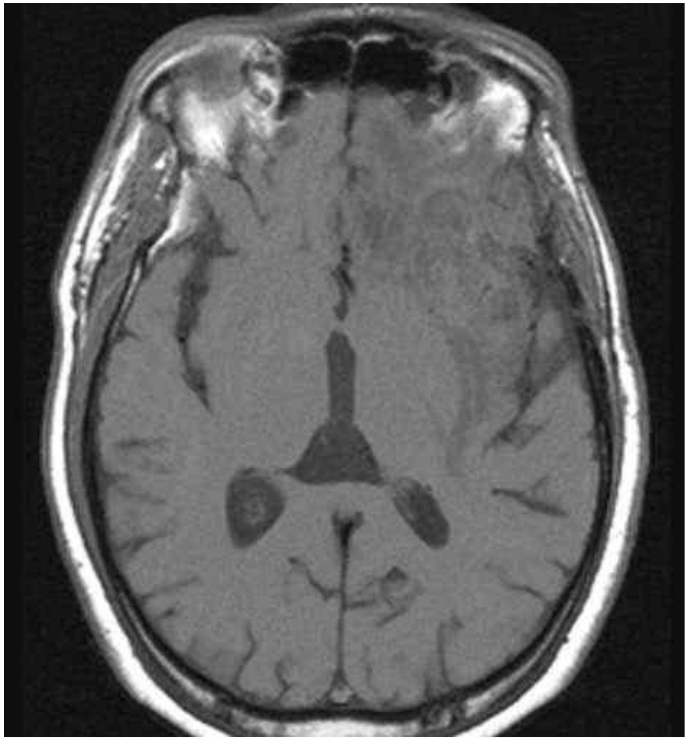
Anaplastic astrocytoma



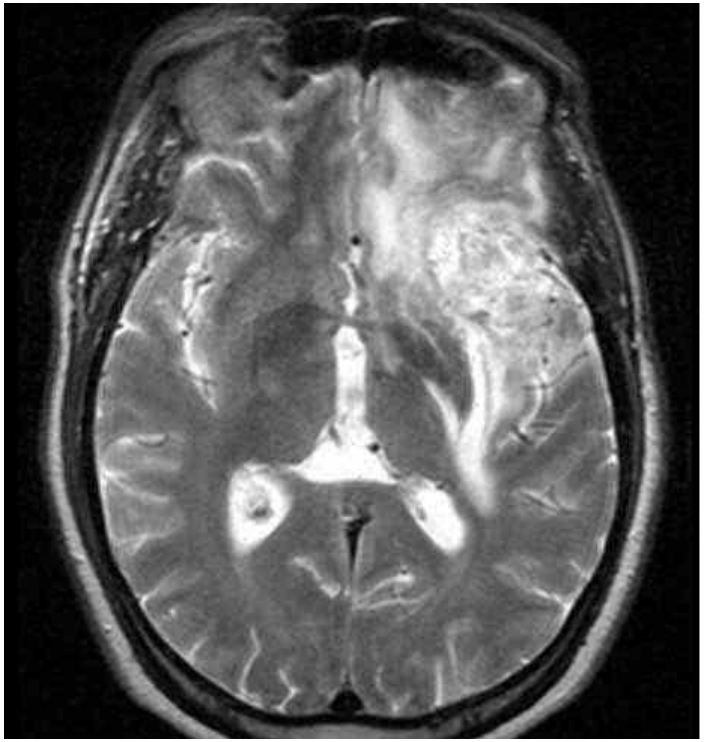
Gliobastoma multiforme

- The most malignant tumor of CNS
- Rapid progression
- 5. a 6. decade
- Deep part of hemispheres (bazal ganglia, talamus, white matter)
- Spreading by CSF (corpus callosum infiltration, spreading on the other side, infiltration of meninges)
- MTS also outside of CNS
- CT scan – cystic, necrosis, heamorrhages

Glioblastoma multiforme

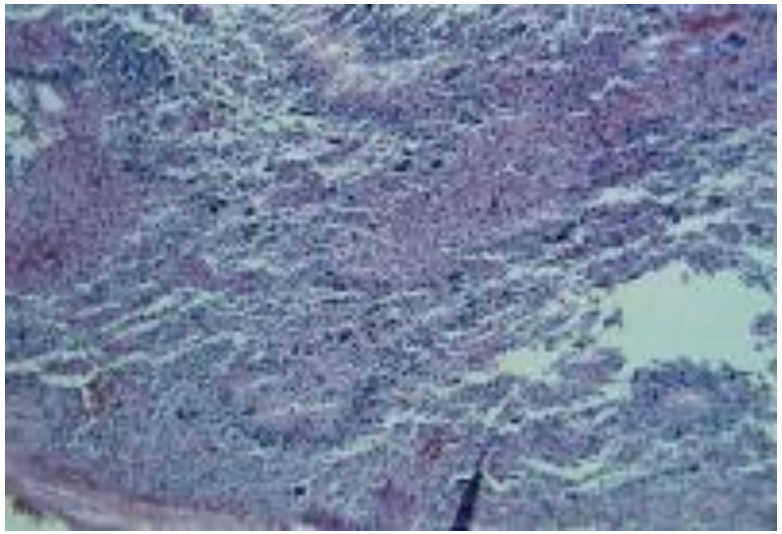


MRI T1 weighted



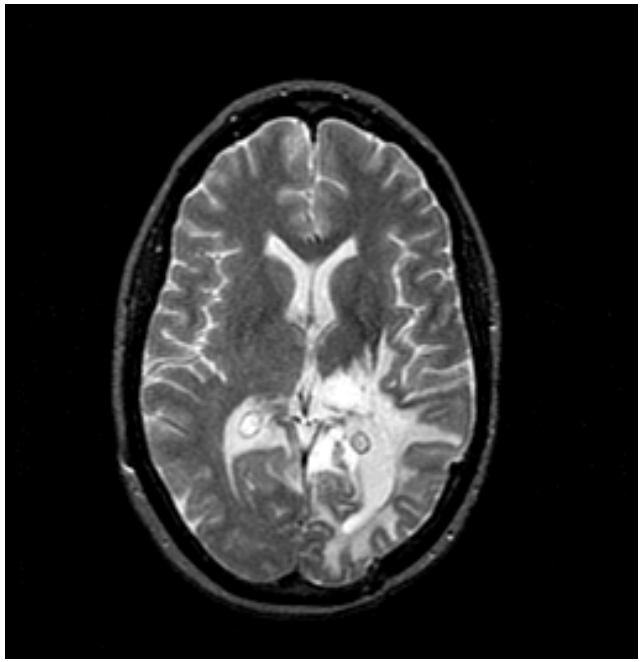
T2 weighted

Glioblastoma multiforme

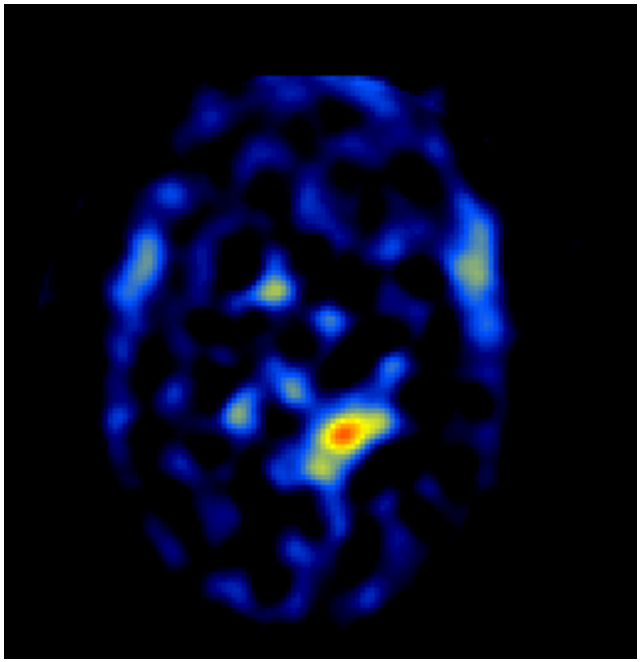


Frequent mitosis
Atypic cells
Neovascularisation
Bleeding

Glioblastoma multiforme

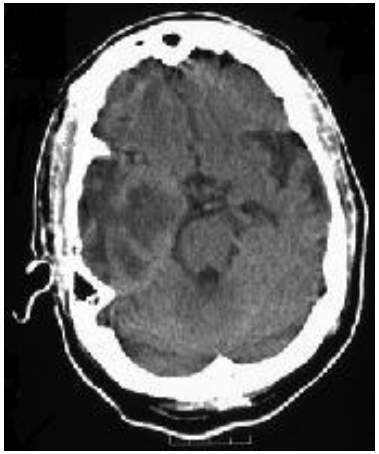


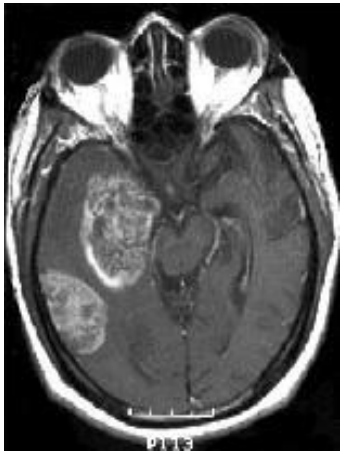
MRI T2 weighted

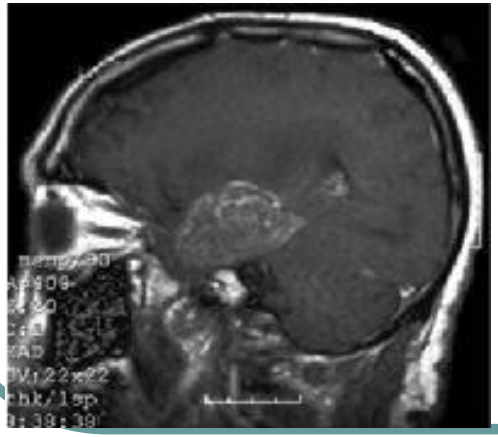


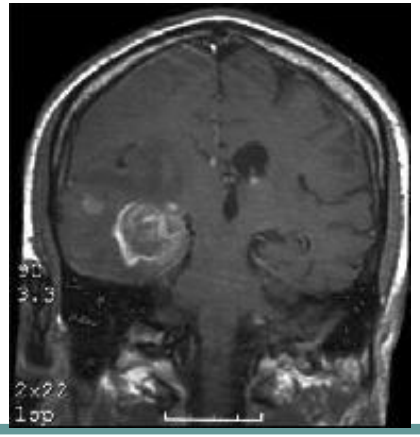
SPECT

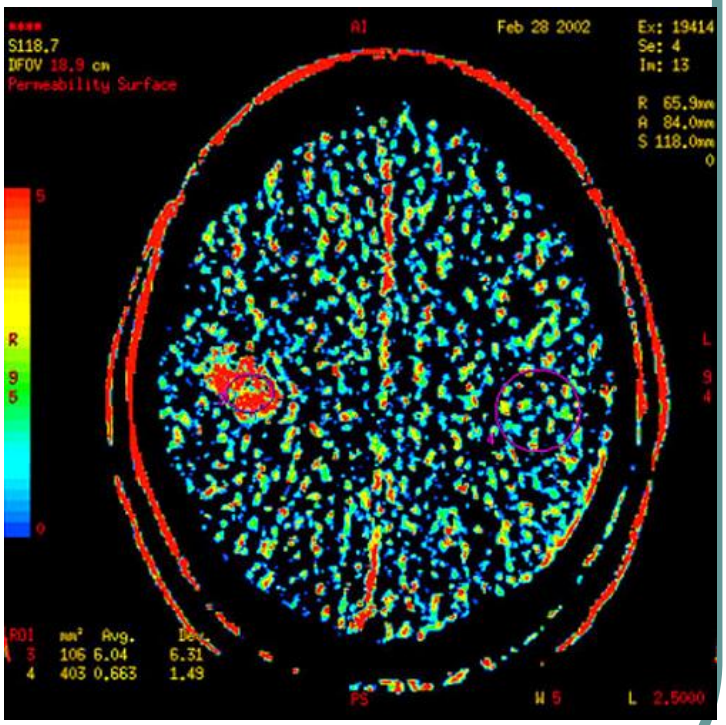
Glioblastoma multiforme











I. Neuroepitelial tumors

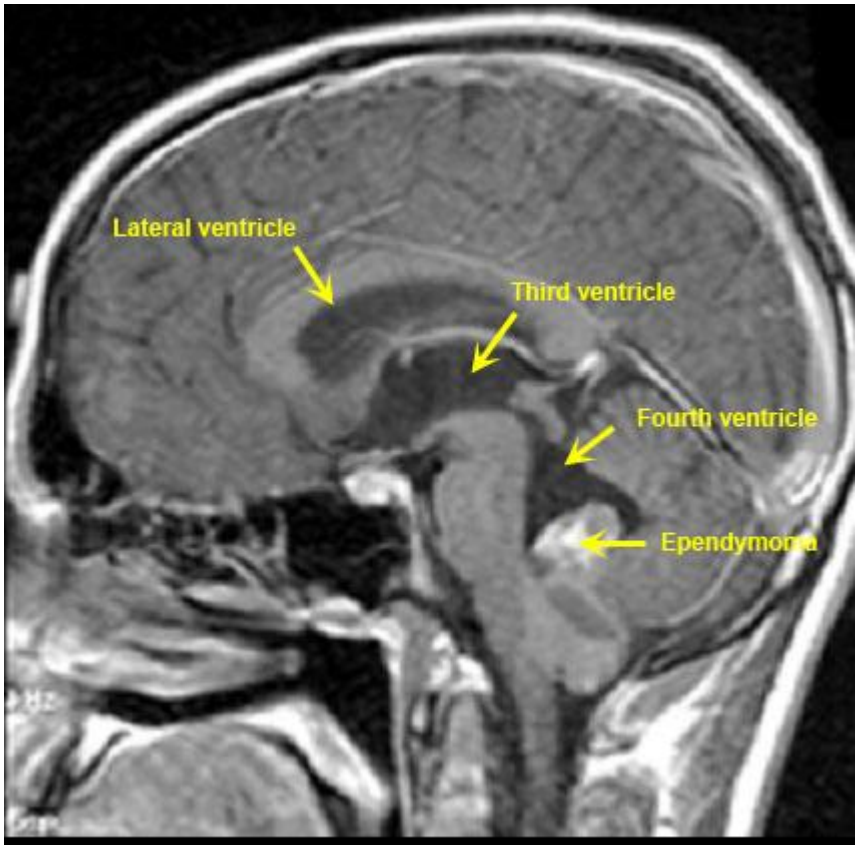
- **Oligodendroglial tumors**
- Adults
- Frequently with calcifications
- Frontal lobe
- 5% of CNS tumors
- Low % is histological malignant

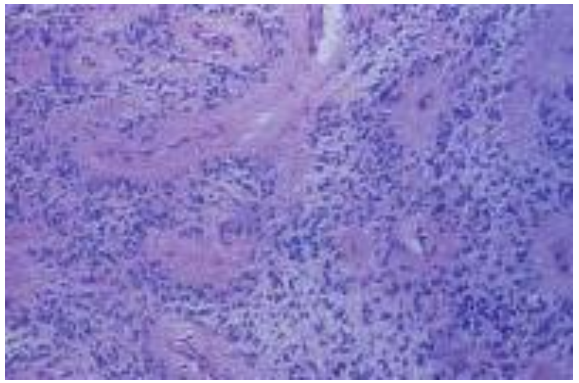
I. Neuroepitelial tumors

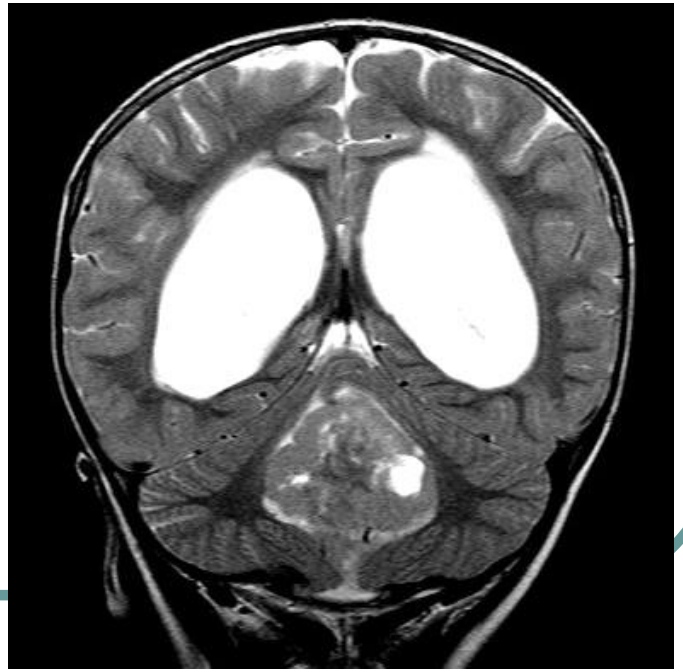
Ependymal cells tumors

- 4% of CNS tumors
- Adults, children
- IV. Ventricle – obstructive hydrocefalus
- Spreading by CSF
- MTS in CNS

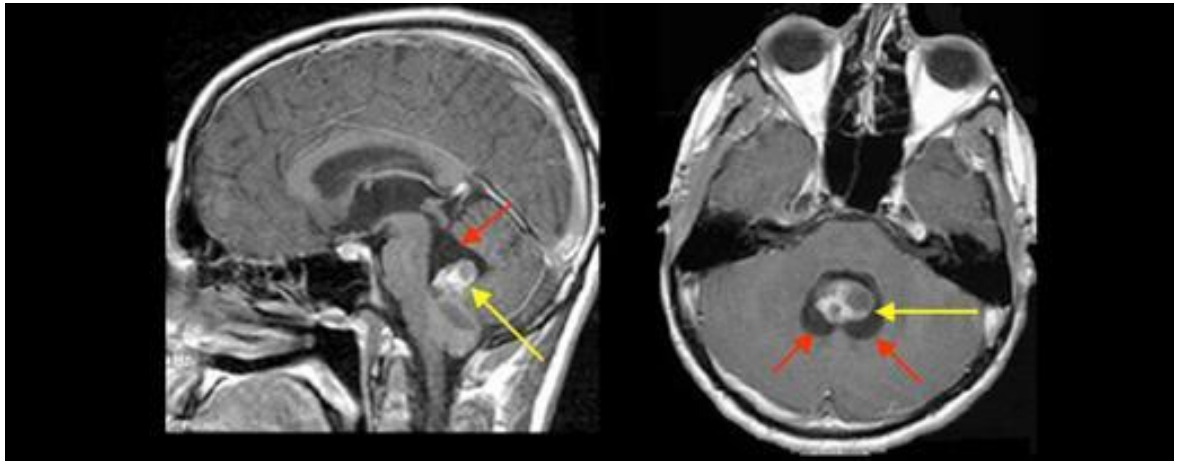
Ependymoma


Lateral ventricle
Third ventricle
Fourth ventricle
Ependymoma





Ependymoma



Post-contrast sagittal T1 Wtd MRI

A

Post-contrast axial T1 Wtd MRI

B

Findings:

An enhancing intra IV ventricular tumor (yellow arrow in figures A, B) is seen. Red arrows point to expanded IV ventricle.

Diagnosis:

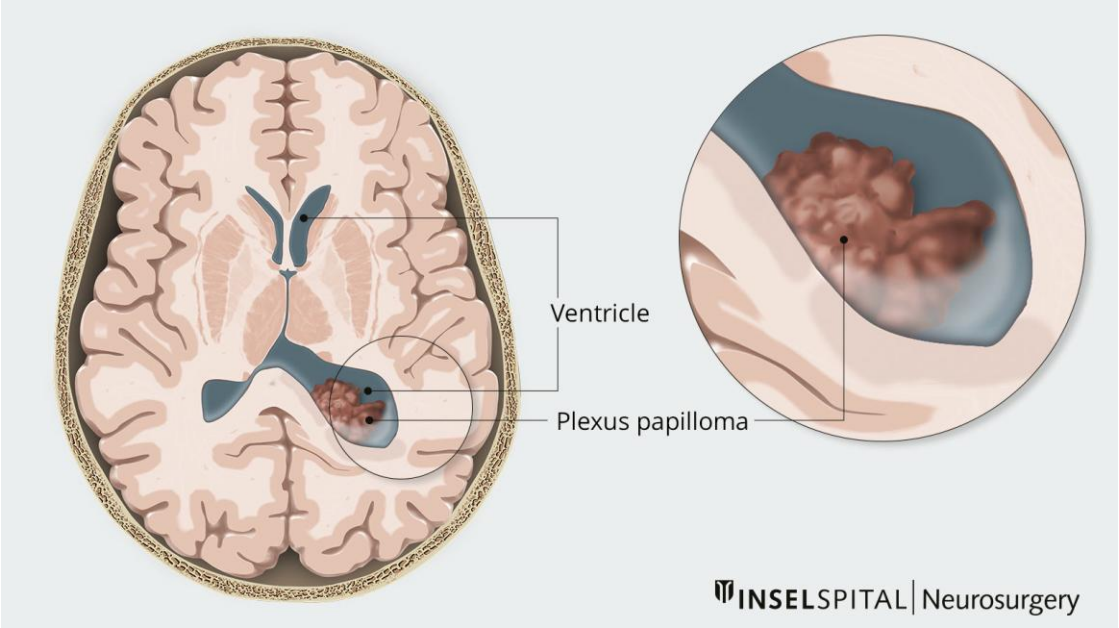
EPENDYMOMA OF THE IV VENTRICLE

- Common pediatric brain tumor
- Enhancing tumors. Calcification can be seen in 50% of tumors.

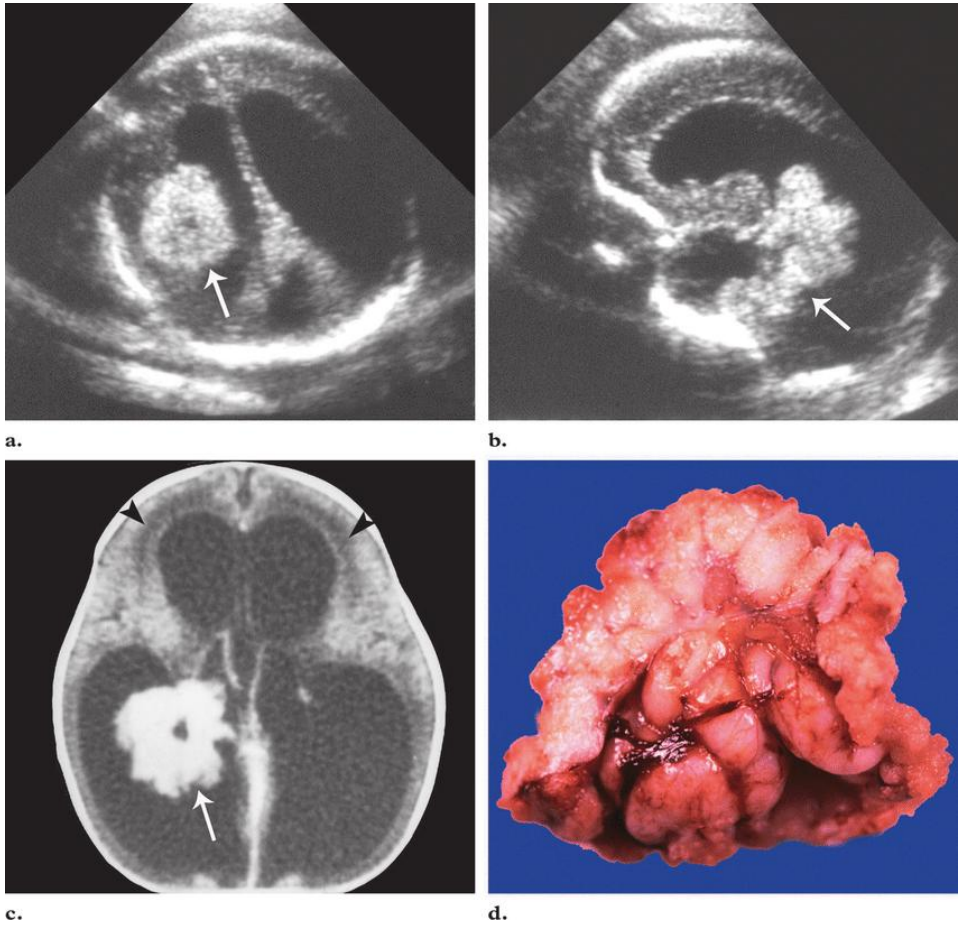
Plexus choroideus tumors

- Papiloma or papilocarcinoma
- Rare
- Childhood
- Localised in ventricles
- Hydrocefalus

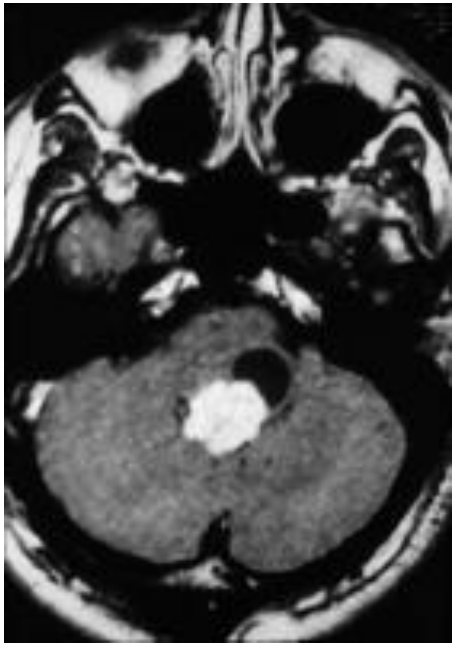
Plexus choroideus tumors



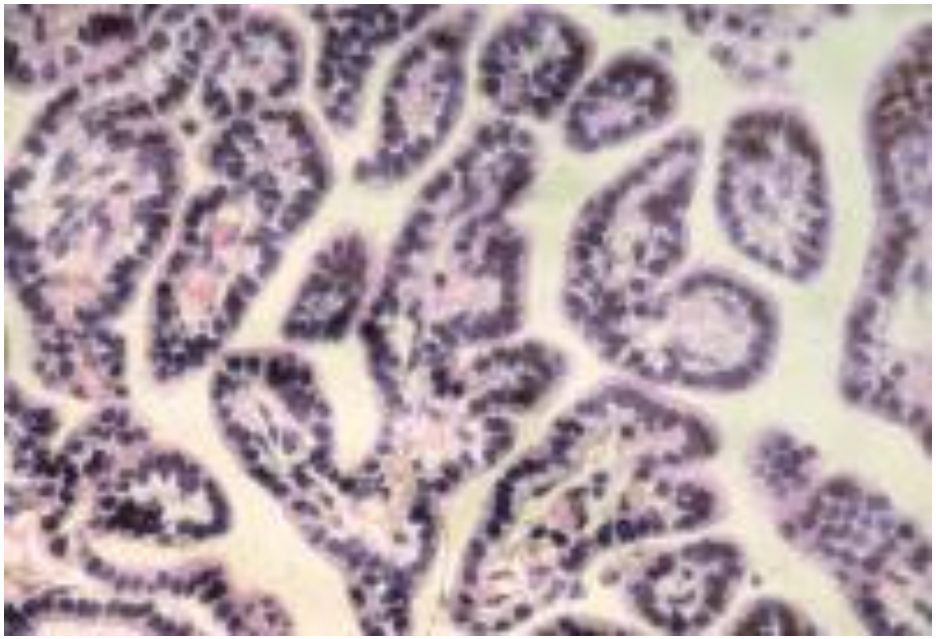
Plexus choroideus tumors



Plexus choroideus tumors



MRI

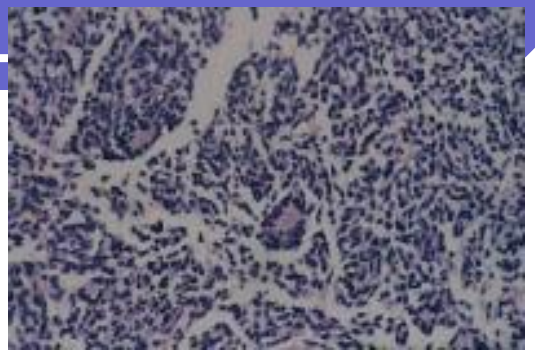


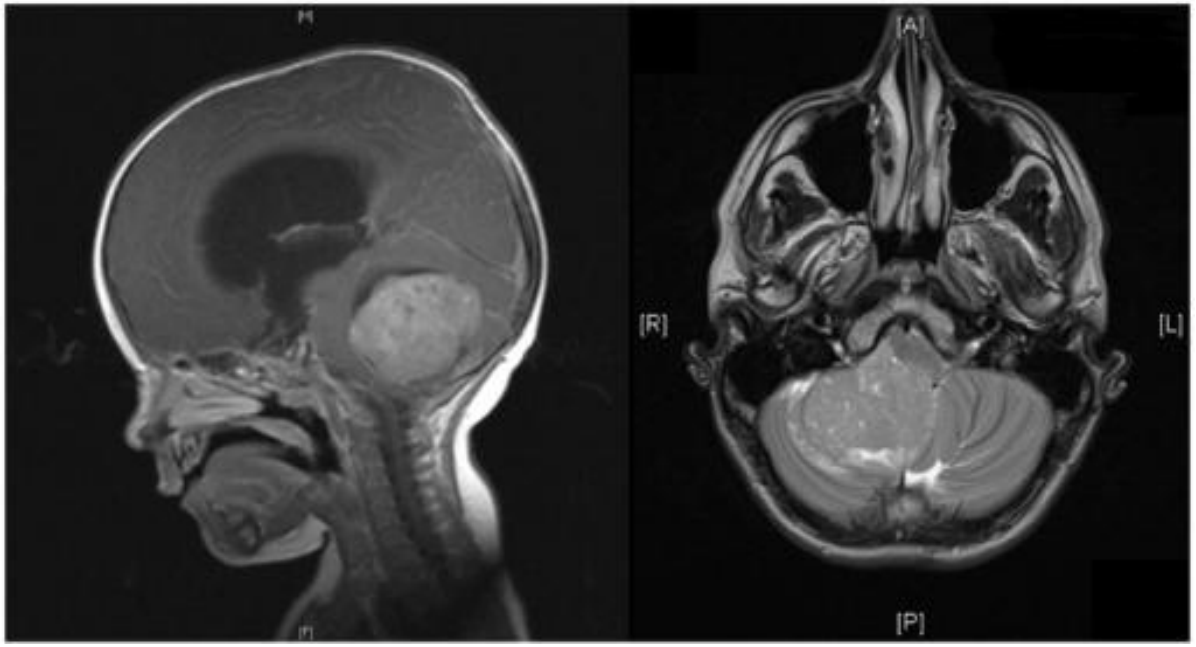
histology

Medulloblastoma

- High grade of malignity
  - 23% of CNS tumors in childhood
  - Vermis, cerebellar hemispheres
  - **Rapid growth**, rapid progression, compression of CSF pathways, **hydrocephalus**, intracranial hypertension
  - MTS in brain and outside of CNS – bones, lymphatic nodes
  - Treatment involves a combination of surgical removal, radiotherapy and chemotherapy, with a 5-year survival rate of 60–80%.

Meduloblastoma

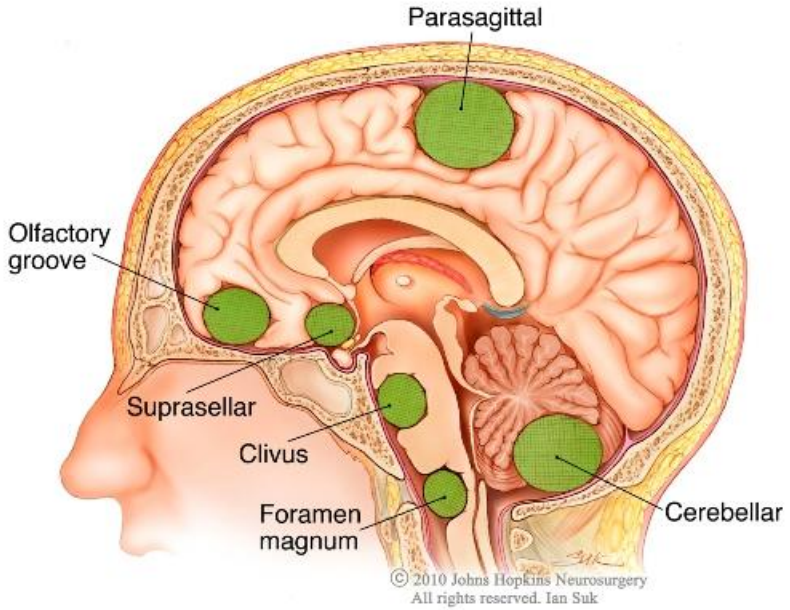


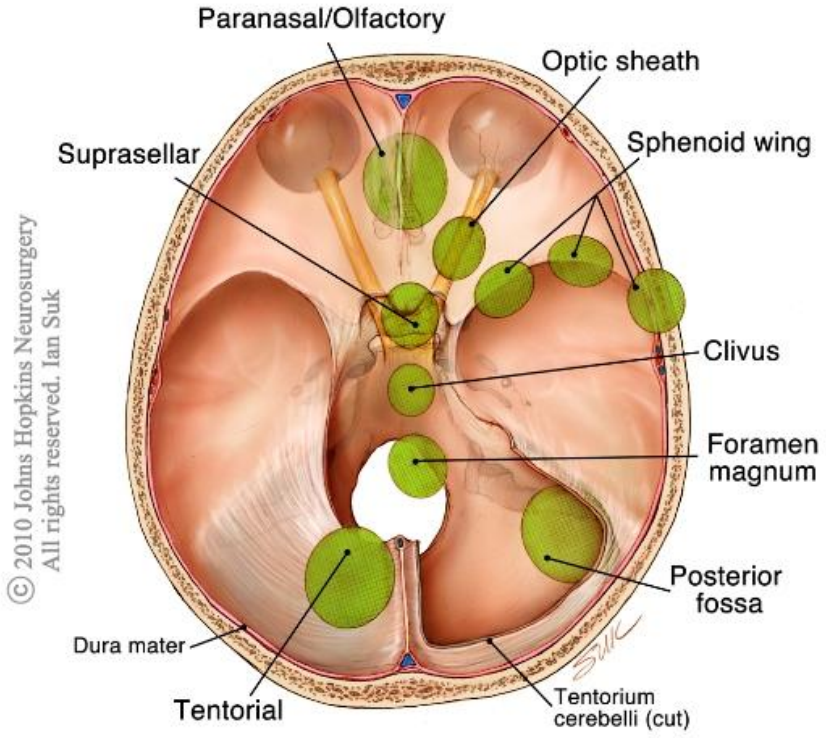


Meningiomas

- 15% of brain tumors
- The most often benign tumors
- 5. decade
- Localisation - hemisphers convexity, parasagital, n. olfactorius, sella turcica, pontocerebellar angle, tentorium
- Mostly benign
- Bone usuration or hyperostosis

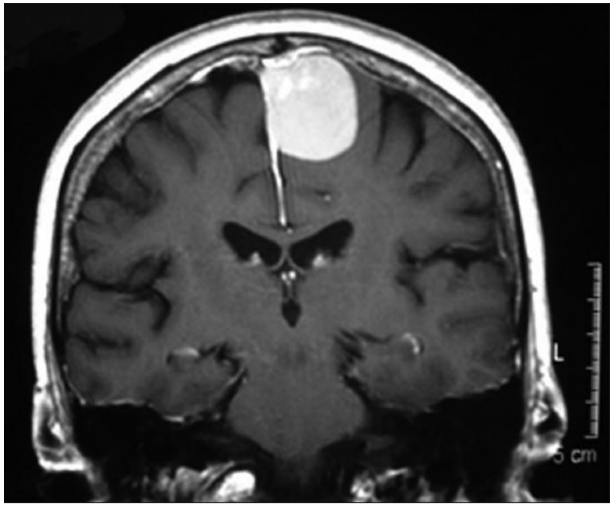
Meningiomas - localisation

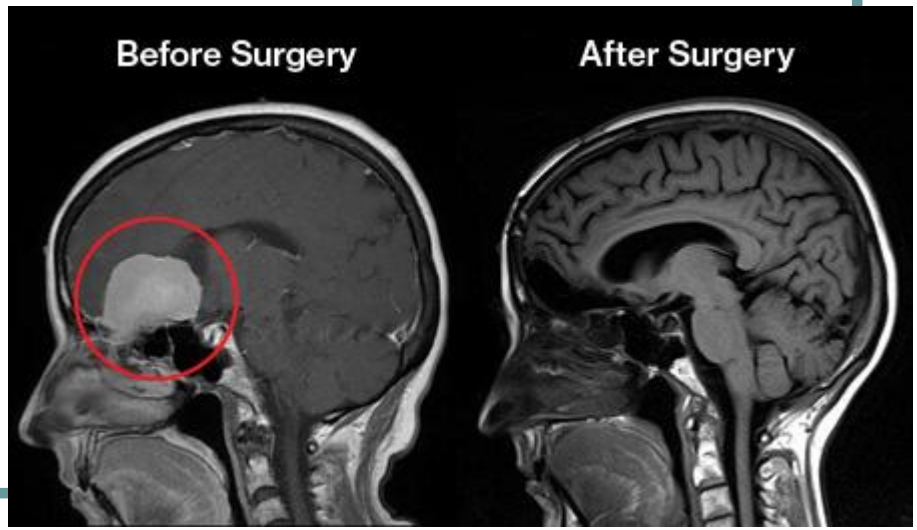




Meningioma

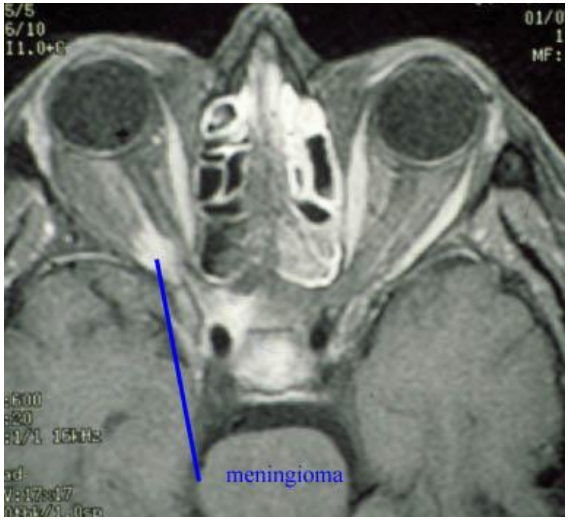
- Parasagital
  - Monoparesis of contralateral lower extremity or paraparesis
- Near bulbus olfactorius
  - Unilateral anosmia





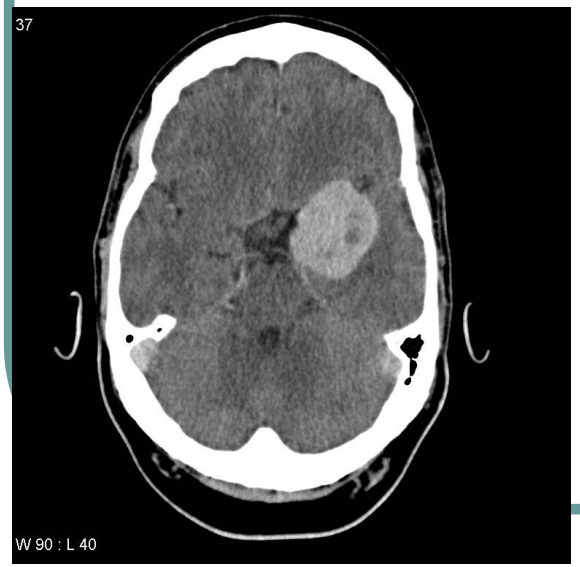
Meningioma

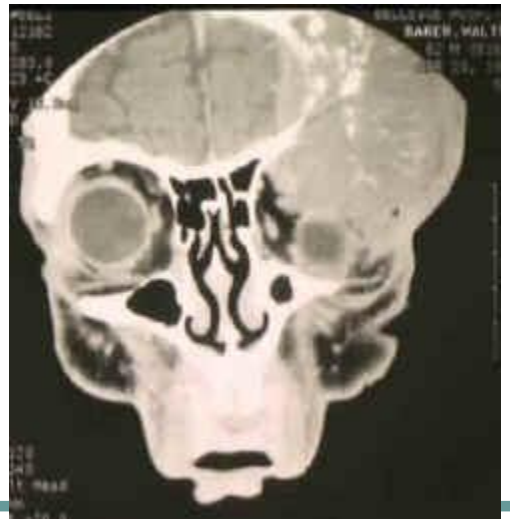
- Near optic nerve
  - Exoftlamus, monocular blindnsess

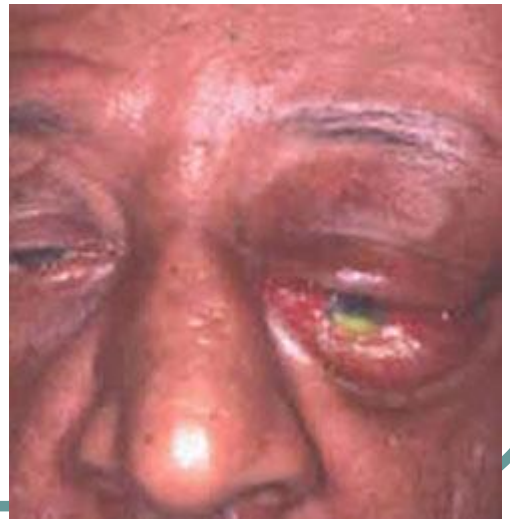


Meningioma

- Near sphenoidal bone wings
  - Epileptic seazures, lesion of cranial nerves – process near fissura orbitalis superior

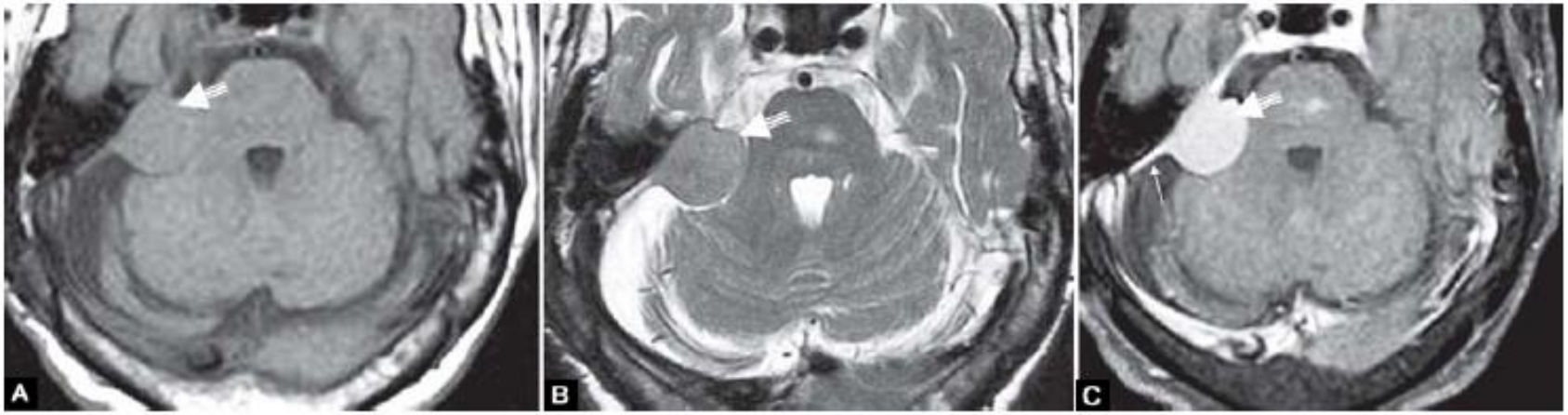






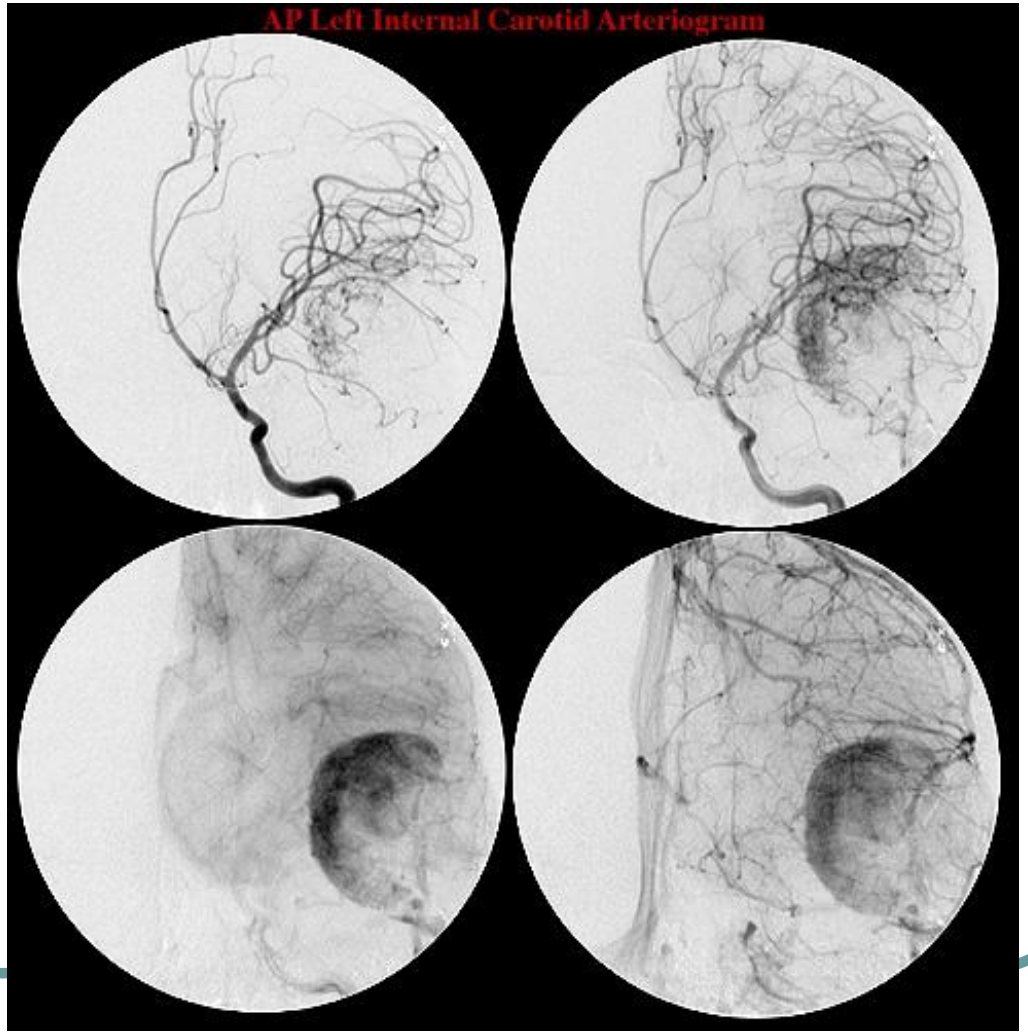
Meningioma

- Pontocerebellar angle
  - Loss of hearing, dizziness, Bells palsy, sensitivity disorders

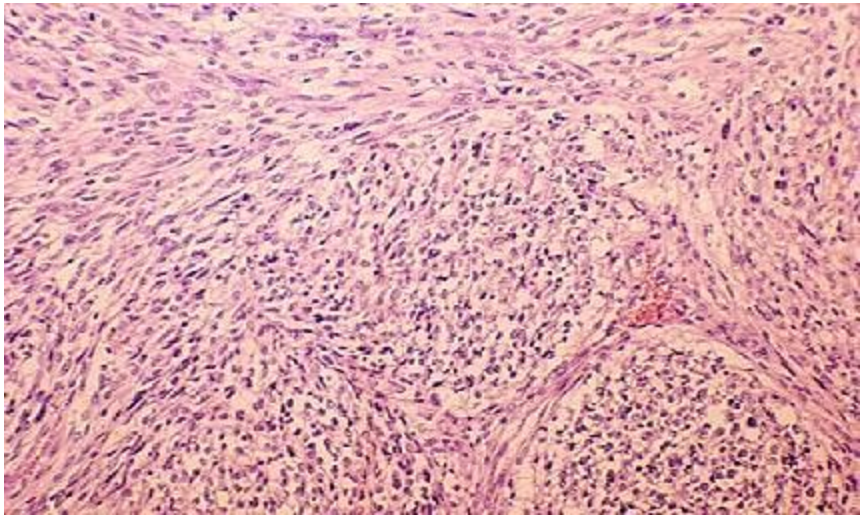


Meningioma

Angiography



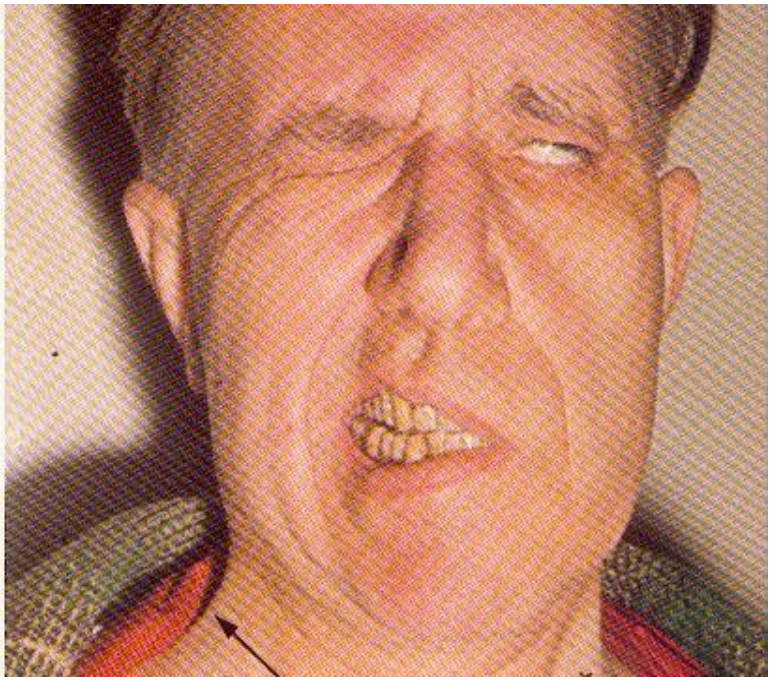
Meningioma



Histology

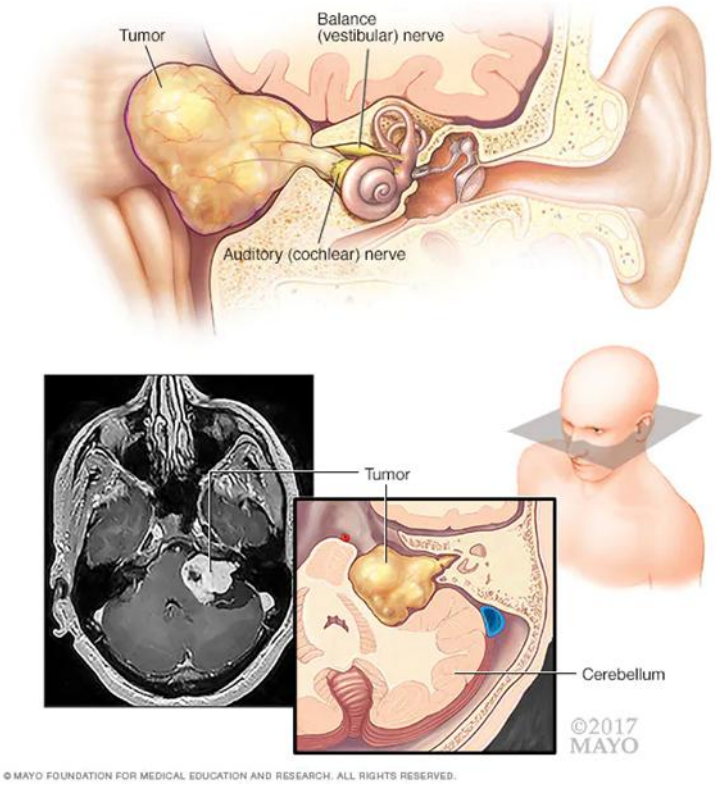
Meningioma

loss of hearing, Bell palsy, n.V. lesion



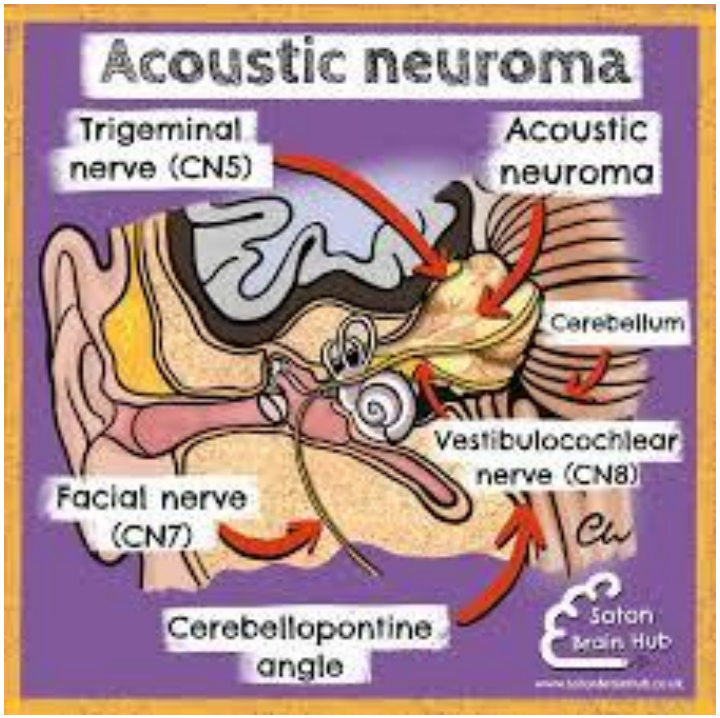
Neurinomas

- Acoustic neuromas
- noncancerous, usually slow growing tumors that form along the branches of the eighth cranial nerve (also called the vestibulocochlear nerve).



Neurinomas - Acoustic neuromas

- N. VIII. play important roles in both hearing and balance.
- Symptoms:
- hearing loss in one ear (unilateral) is the initial symptom in approximately 90 percent of affected individuals.
- ringing in the ears (tinnitus) and dizziness or imbalance.
- Neurinoma can compress
- n.VII – Bell´s palsy
- N.V. – sensitivity disorders
- Cerebellar hemisphere - ataxia

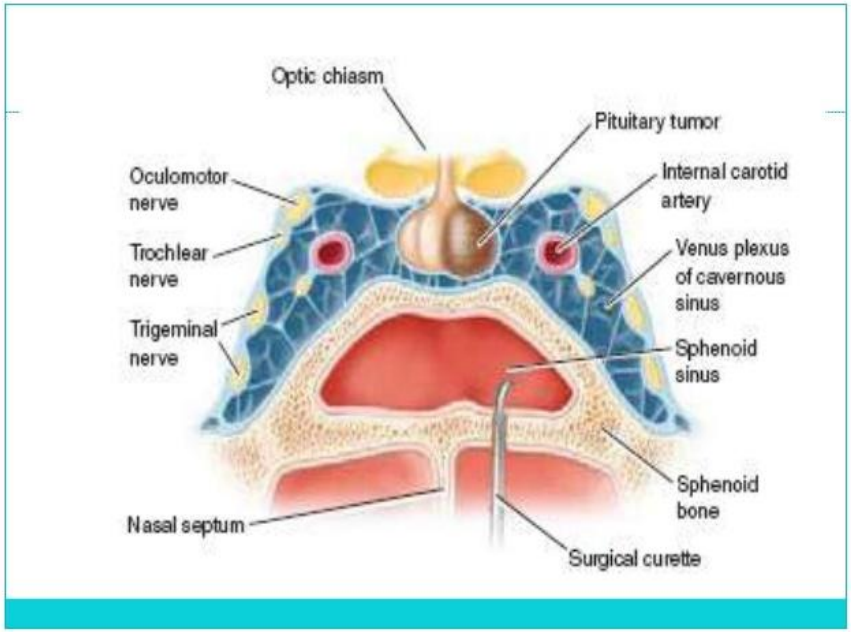


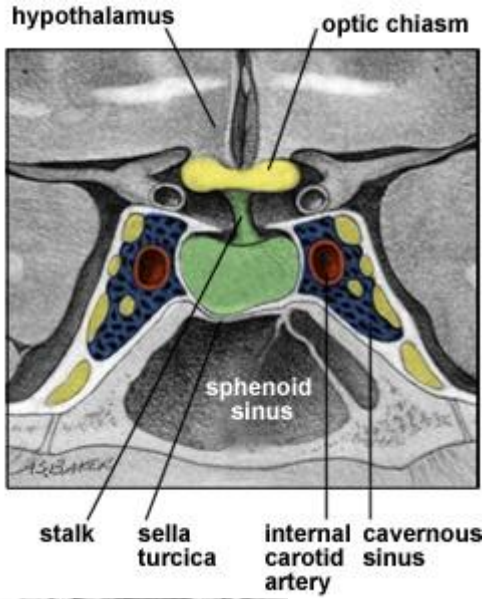
Tumors of sellar region

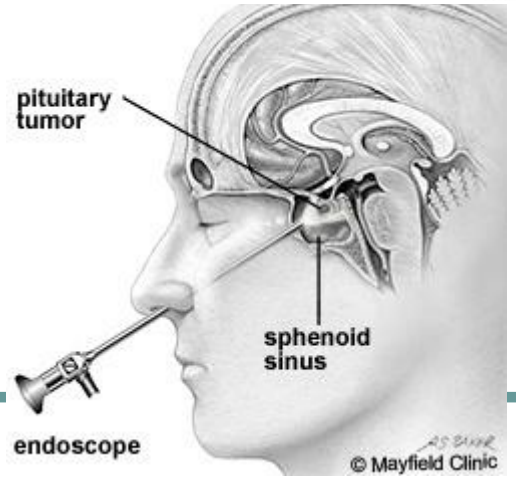
- Adenoma, adenocarcinoma
- Chiasma opticum compression – bitemporal hemianopsy
- Endocrinological symptoms

- Skull X-ray – enlargment of sella turcica

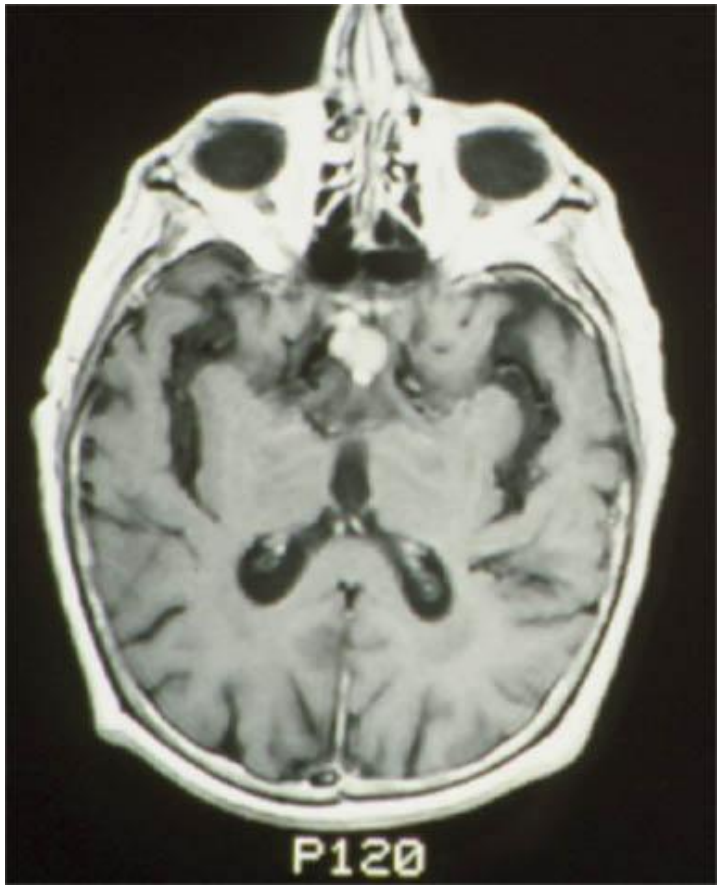
Tumors of sellar region

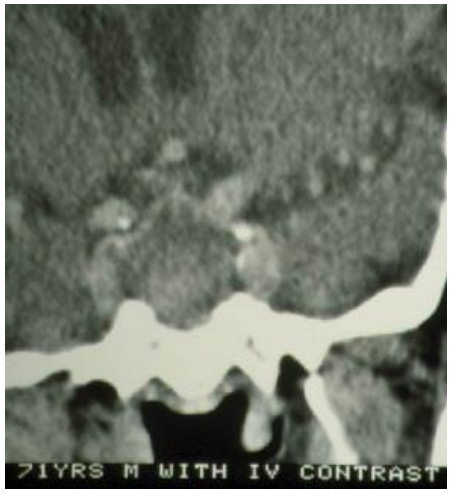


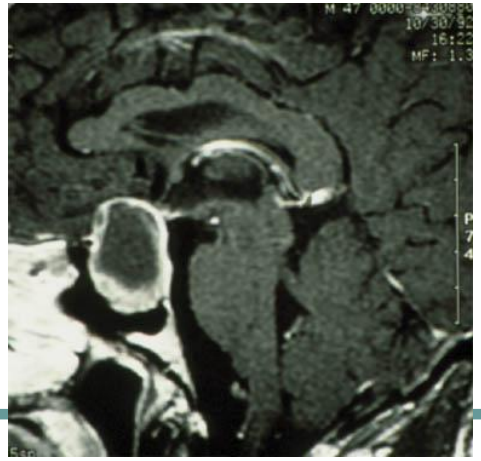




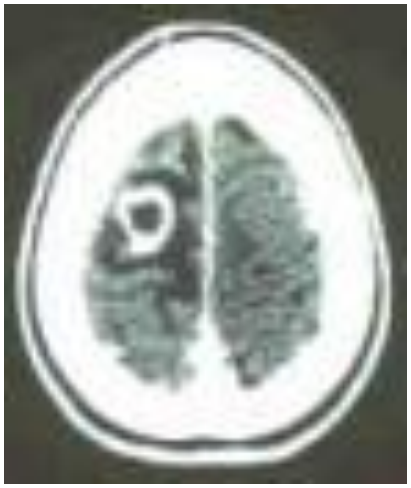
Tumors of sellar region



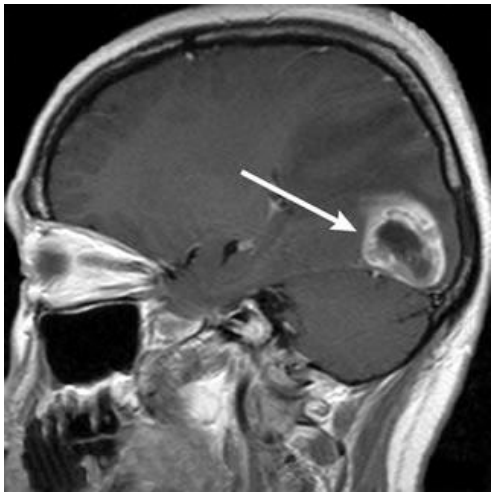


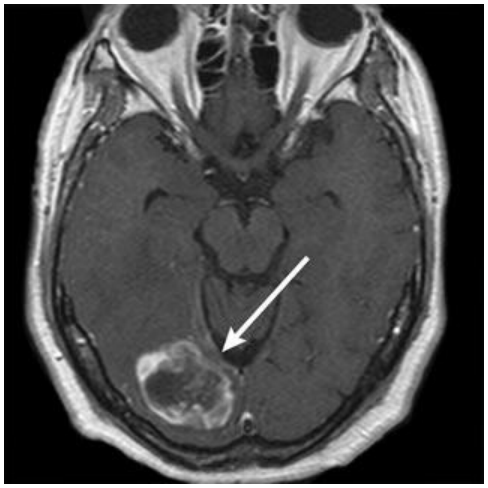


Secondary tumors - MTS



CT





MRI

Meningeal carcinomatosis

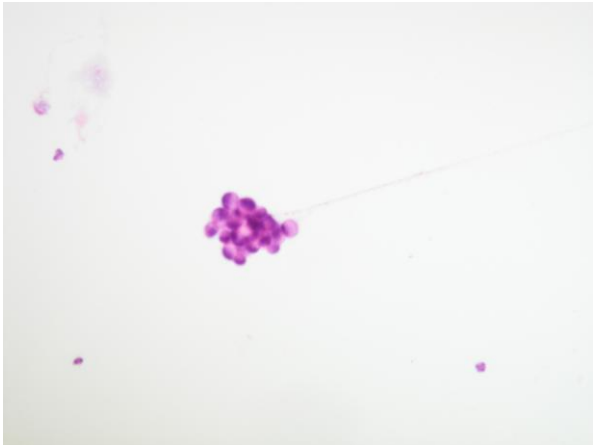
- A rare manifestation of malignant diseases
- Pure MC – affects the leptomeninges without affecting other parts of the CNS
- Involvement of the meninges – focal, multifocal, diffuse

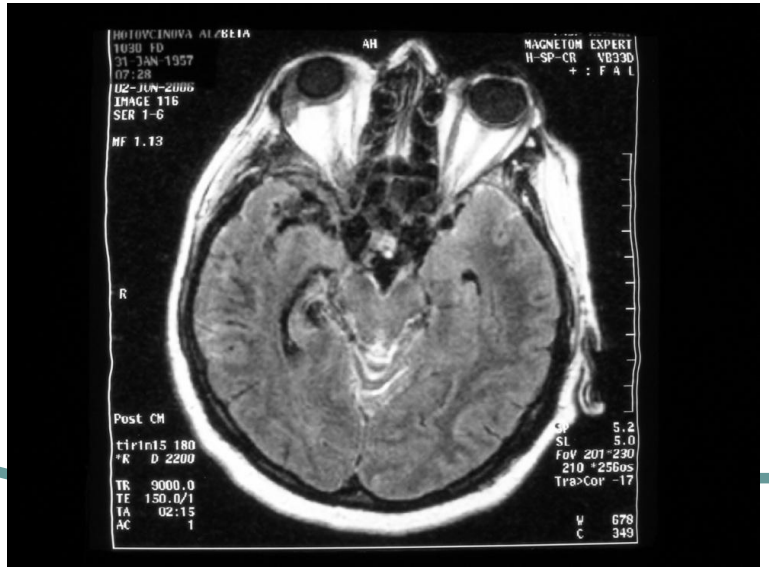
Meningeal carcinomatosis

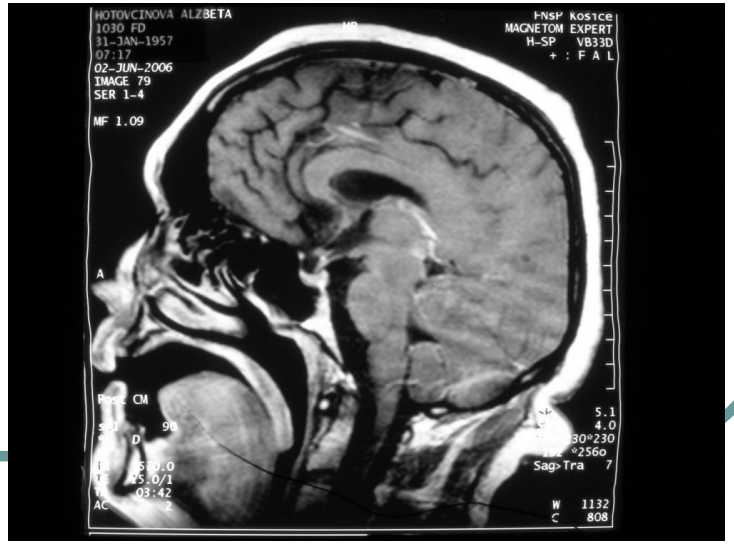
- Incidence - increases with the prolongation of survival of patients with malignant diseases
- Nevertheless, due to the variability of clinical symptomatology, ante mortem diagnosis is difficult
- Diagnostic significance – the presence of malignant cells in the cerebrospinal fluid

Meningeal carcinomatosis

- **Symptoms**
- Headache
- Meningeal syndroma
- CSF – hypoglykorhachia, increased proteins, malignant cells
- MRI – with gadolinium





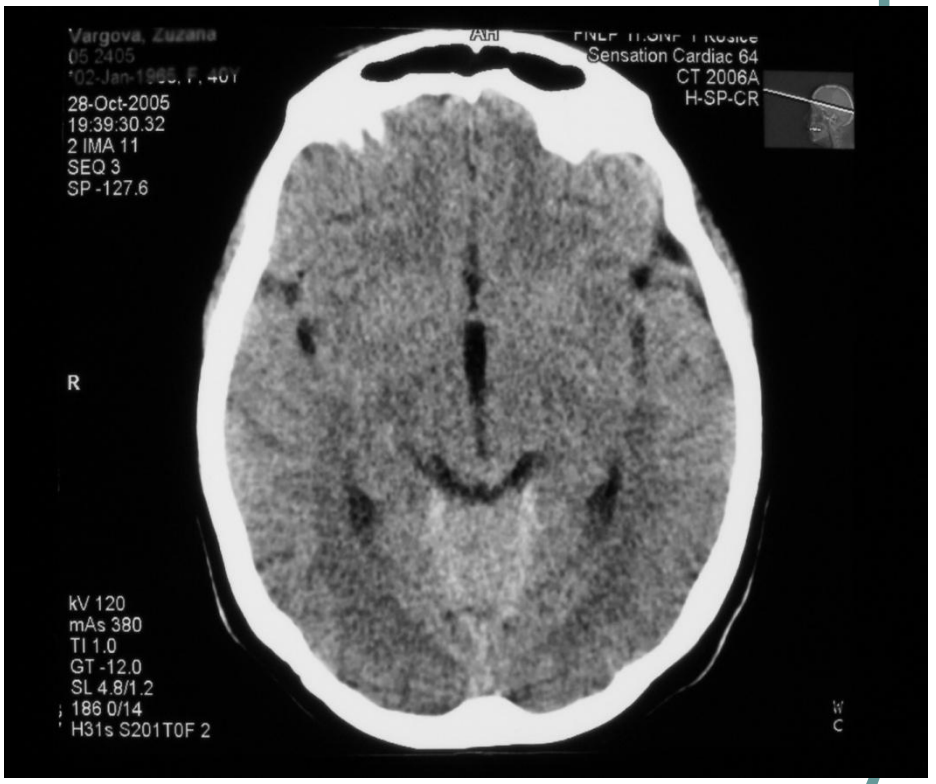


Case study

- 40 – years old woman
- History – negative
- august 2005 – back pain - lumbosacral
- october – pain – cervical region, lower extremities weakness
- Meningeal syndroma
- CSF – clear, colorless, glykorhachia – 0.6 ..0.7 mmol/l, (glycemia: 8,7 mmol/l), proteins – 1355 mg/l, seg 6/3, Ly 66/3.

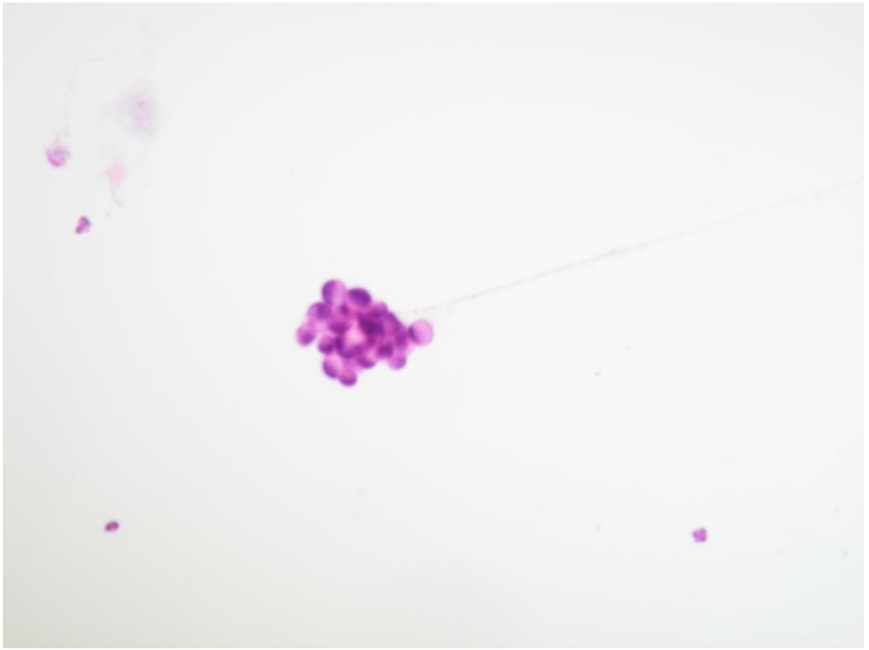
Case study

- Dif.dg.
- TBC meningitis
- Meningeal carcinomatosis
- 28.10. – CSF: proteins: 2375 mg/l, glykorhachia 1,1 mmol/l, Erytrocytes
- Brain CT – negative



Case study

- 29.10. psychomotor disorder, oculomotor disorders - upward deviation of the bulbs
- 30.10. exitus lethalis
- CSF – october 30
- activated monocytes and erythrophages, atypical cells meeting the criteria of malignancy – malignant carcinoma cells

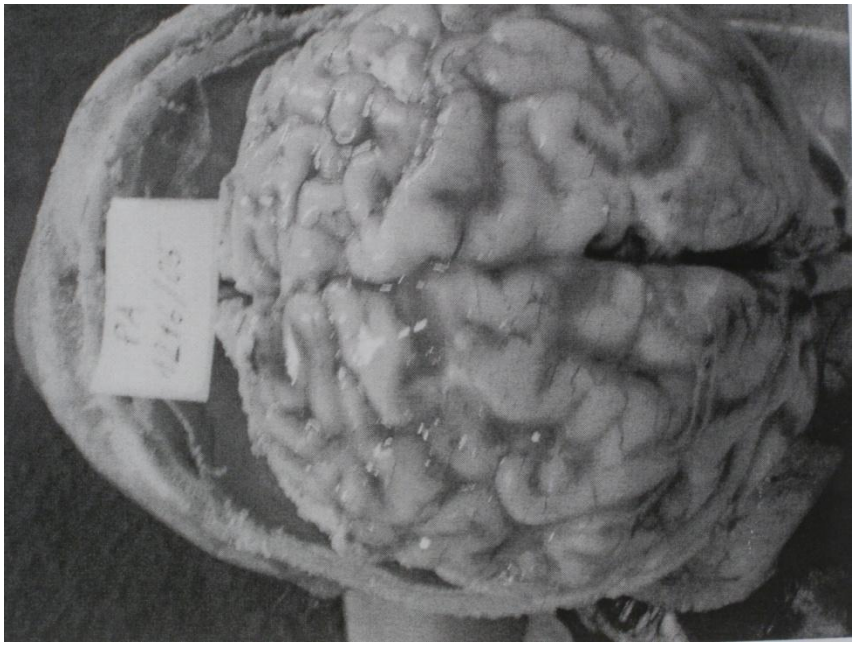


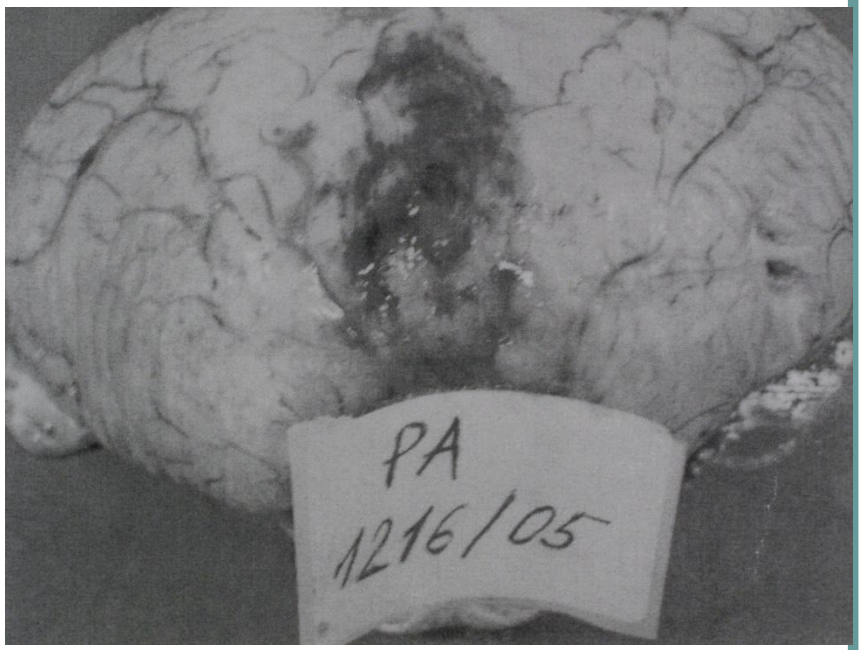
Case study

- Autopsy
- Gastric adenocarcinoma

- MTS to Lymph nodes
- MTS ovaries
- peritoneum infiltration
- carcinomatous infiltration of the leptomeninges, adenohypophysis, brain, cerebellum

Case study - autopsy





Diagnosis

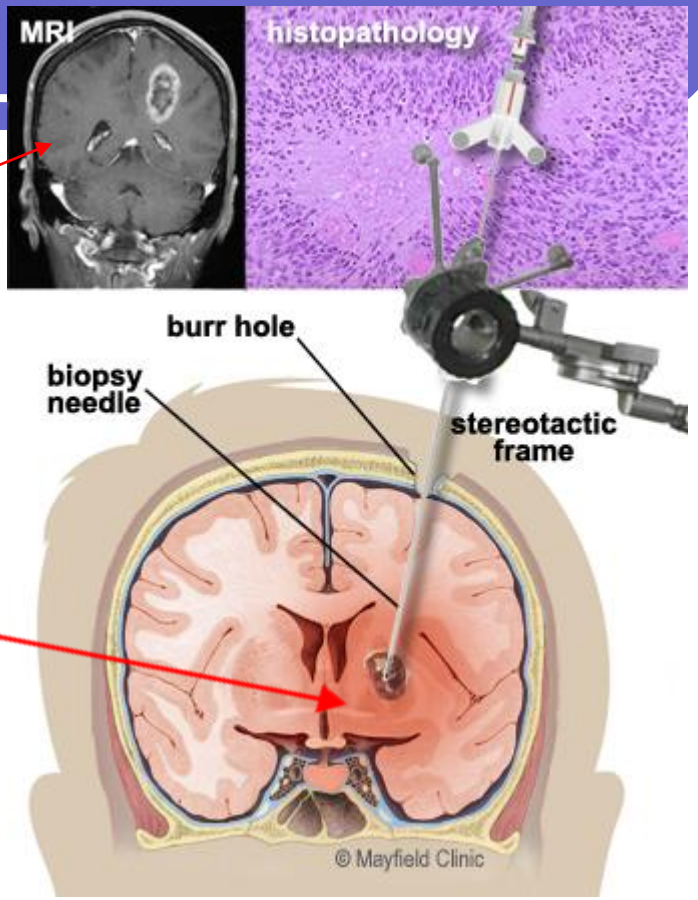
- Slowly progressive focal neurological signs and signs of intracranial hypertension, epilepsy in a patient with hegative history of epilepsy
- Imaging
  - CT
  - MRI
  - Skull X-ray
- Angiography
- EEG
- Histological examination of brain tumor tissue samples obtained either by means of brain biopsy or open surgery – definitive diagnosis

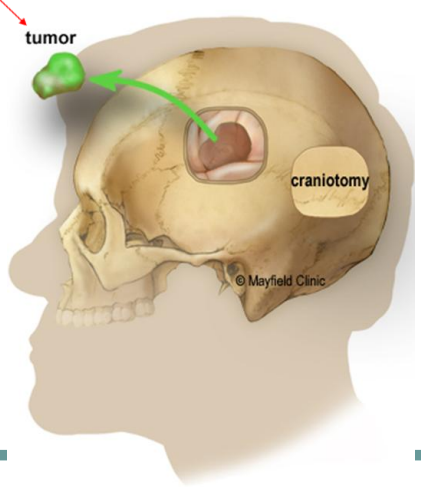
Diagnosis

- Clinical feature
- Imaging
- Histology

biopsy

Kraniotomy



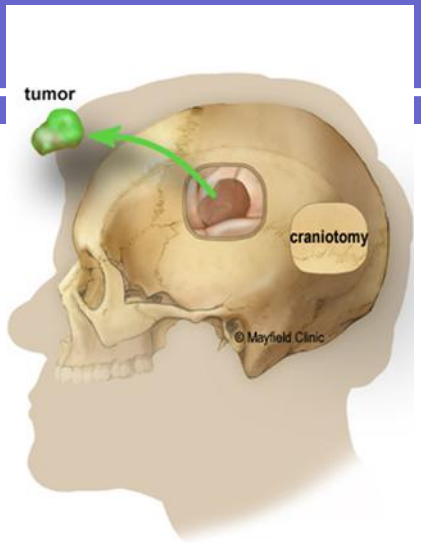


Treatment

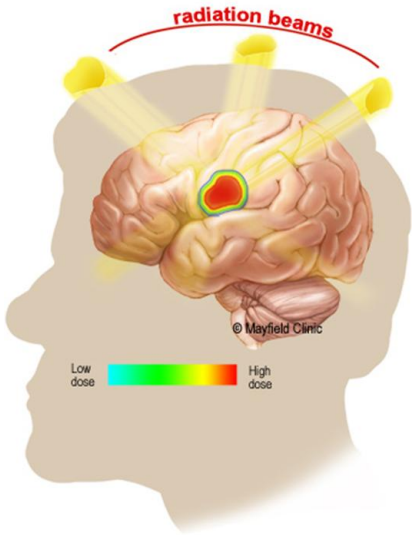
- Treatment of ICH syndrome (antiedematous, antiemetics, analgesics)
- Surgical
- Conventional – total or partial resection
- Gamma knife
- Conservative
- Radiotherapy
- Chemotherapy

Treatment

- Surgery – kraniotomy

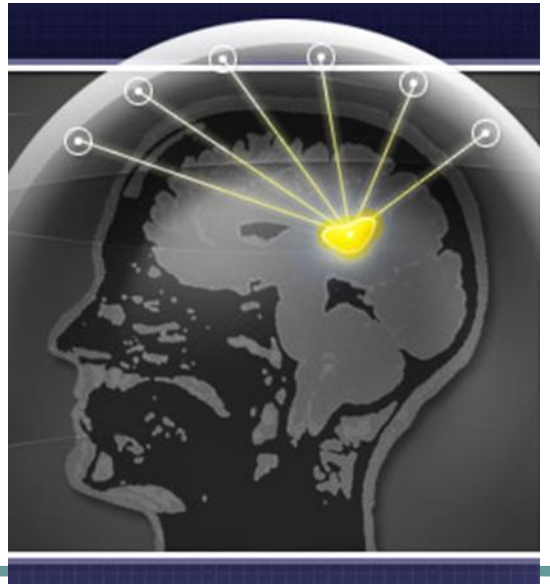


- Stereotaktic surgery – gamma knife



Stereotactic radiosurgery

- A machine rotates around the patient, aiming radiation beams at the tumor.
- A high dose of radiation during a single session.
- Fractionated radiotherapy delivers lower doses of radiation over many visits.
- Whole brain radiotherapy (WBRT) delivers the radiation dose to the entire brain. It may be used to treat multiple brain tumors and metastases.



Idiopatic intracranial hypertension

- Previously - pseudotumor cerebri

- syndrome of intracranial hypertension without the presence of an expansive process
- it is manifested by visual impairment due to bilateral papilledema of the optic nerve

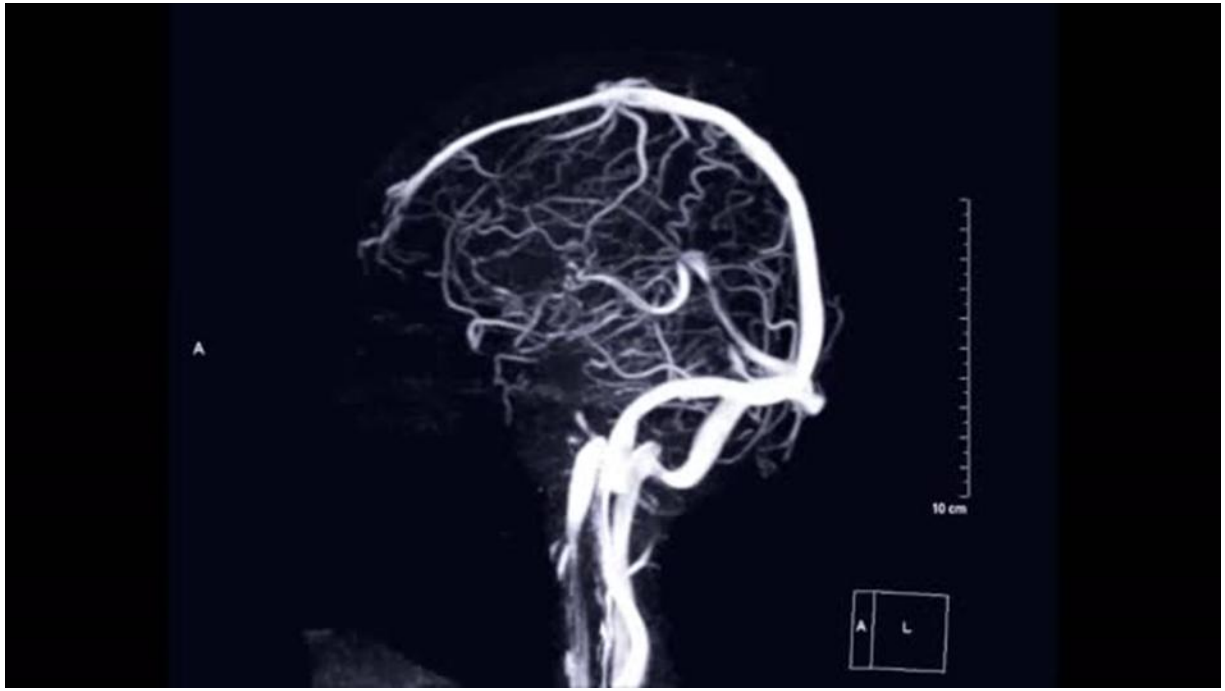
Idiopatic intracranial hypertension

- Symptoms of increased intracranial pressure
- Headache - can be pulsating, can be accompanied by nausea and vomiting, can be increased by sneezing and coughing
- Pulsating tinnitus
- Diplopia in a horizontal line
- Symptoms of papilledema
- Progressive loss of the peripheral visual field
- Blurred vision to blindness
- Sudden blindness due to intraocular hemorrhage due to pathological neovascularization present

Idiopatic intracranial hypertension

- Etiology – unknown, risk factors – obesity, certain medications – tetracycline
- Diagnostics
- Imaging – to exclude other reason, brain MRI including MR venography (to exlude tumor, venous thrombosis)
- Lumbar puncture - to mesure CSF pressure, + to rule out another cause
- Treatment
- Drug of choice – acetazolamide, diuretics, e.g. Furosemide, can also be used
- Weight reduction, low-salt diet
- ventriculoperitoneal shunt may be considered in case of impending vision loss

Idiopatic intracranial hypertension



MR venography

Paraneoplastic neurological syndroms

- Occur in association with cancer, with immune-mediated pathogenesis
- are characterized by the presence of specific neuronal antibodies
- They do not represent direct infiltration of nerve tissue by tumor cells
- 6.6% - 10% of cancer patients

Paraneoplastic neurological syndroms

Table 1 High-Risk Antibodies (>70% Associated With Cancer)

Antibody (alternative name)	Neurologic phenotypes	Frequency of cancer (%)	Usual tumors	Sex, age-related, and other specificities
Hu (ANNA-1)[8]	SNN, chronic gastrointestinal pseudo-obstruction, EM, and LE	85	SCLC >> NSCLC, other neuroendocrine tumors, and neuroblastoma	LE is usually nonparaneoplastic in patients aged <18 y[18]
CV2/ CRMP5[30,e17,e40,e41]	EM and SNN	>80	SCLC and thymoma	Patients with an associated thymoma are younger and present more frequently MG and less commonly neuropathy
SOX1[36,e42]	LEMS with and without rapidly progressive cerebellar syndrome	>90	SCLC	Stronger correlation with SCLC than with a particular neurologic presentation
PCA2 (MAP1B) [57,e43,e44]	Sensorimotor neuropathy, rapidly progressive cerebellar syndrome, and EM	80	SCLC, NSCLC, and breast cancer	
Amphiphysin[31,e18]	Polyradiculoneuropathy, SNN, EM, SPS	80	SCLC and breast cancer	Associated antibodies commonly coexist. Patients with isolated antiamphiphysin → women, with breast cancer and SPS
Ri (ANNA-2)[20,26]	Brainstem/cerebellar syndrome, OMS	>70	Breast > lung (SCLC and NSCLC)	Breast cancer in women; lung cancer in men
Yo (PCA-1)[21,e19]	Rapidly progressive cerebellar syndrome	>90	Ovary and breast cancers	Almost all female; in men, antigen expression by tumor should be proven
Ma2 and/or Ma[45,e15,e45]	LE, diencephalitis, and brainstem encephalitis	>75	Testicular cancer and NSCLC	Young men → testicular tumors and isolated Ma2 positivity; older patients → SCLC and both Ma1/2 positivity
Tr (DNER)[22,23]	Rapidly progressive cerebellar syndrome	90	Hodgkin lymphoma	
KLHL11[48-50]	Brainstem/cerebellar syndrome	80	Testicular cancer	Young men

Abbreviations: ANNA = antineuronal nuclear antibody; CRMP5 = collapsin response-mediator protein 5; DNER = delta/notch-like epidermal growth factor–related receptor; EM = encephalomyelitis; KLHL11 = Kelch-like protein 11; LE = limbic encephalitis; LEMS = Lambert-Eaton myasthenic syndrome; MAP1B = microtubule-associated protein 1B; MG = myasthenia gravis; NMDAR = NMDA receptor; NSCLC = non–small-cell lung cancer; OMS = opsoclonus-myoclonus syndrome; PCA = Purkinje cell antibody; SCLC = small-cell lung cancer; SNN = sensory neuronopathy; SPS = stiff-person syndrome.

Paraneoplastic neurological syndroms

Table 2 Intermediate-Risk Antibodies (30%–70% Associated With Cancer)

Antibody	Neurologic phenotypes	Frequency of cancer (%)	Usual tumors	Sex, age-related, and other specificities
AMPAR[16,17,e46]	Limbic encephalitis	>50	SCLC and malignant thymoma	Paraneoplastic origin is more likely when other onconeuronal antibodies co-occur
$GABA_BR$[e14,15,e2,e3,e47-e49]	Limbic encephalitis	>50	SCLC	Paraneoplastic cases are more commonly observed in elderly men, smokers, with associated anti-KCTD16 antibodies. Most of young patients are not paraneoplastic
mGluR5[38]	Encephalitis	~50	Hodgkin lymphoma	
P/Q VGCC[e50,e51]	LEMS, rapidly progressive cerebellar syndrome	50 (LEMS; nearly 90 for rapidly progressive cerebellar syndrome)	SCLC	Co-occurrence with N-type VGCC antibodies might be slightly more common in paraneoplastic LEMS[e52-e54]
NMDAR[40,43,44]	Anti-NMDAR encephalitis	38	Ovarian or extraovarian teratomas	Tumor (mostly ovarian teratomas) predominates in female aged between 12 and 45 y (50%). Elderly patients have less frequently tumors (<25%), but usually they are carcinomas. Paraneoplastic cases in children are very rare (<10%)
CASPR2[51,52]	Morvan syndrome	50	Malignant thymoma	CASPR2 should be considered as intermediate-risk antibody only in the setting of Morvan syndrome. When associated with other neurologic syndromes, the risk of cancer is very low.

Abbreviations: AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; $GABA_BR$ = gamma-aminobutyric acid-b receptor; KCTD16 = potassium channel tetramerization domain containing; LEMS = Lambert-Eaton myasthenic syndrome; mGluR5 = metabotropic glutamate receptor type 5; NMDAR = NMDA receptor; SCLC = small-cell lung cancer; VGCC = voltage-gated calcium channel.

Paraneoplastic neurological syndroms

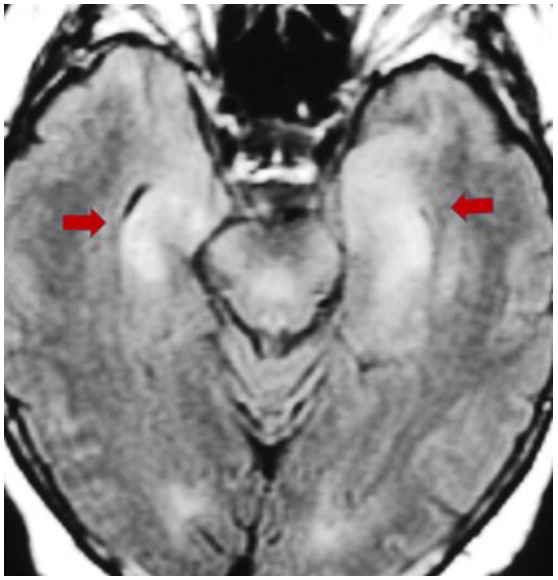
- They can manifest earlier than the malignant disease itself
- they can affect any part of the nervous system
- High-risk phenotypes are:
- encephalomyelitis
- limbic encephalitis
- rapidly progressive cerebellar syndrome
- opsoclonus-myoclonus
- sensory neuronopathy

Paraneopalstic encephalomyelitis

- it is characterized by clinical dysfunction in several parts of the nervous system
- Clinical picture:
- personality changes, depression, seizures, memory disorders
- it is most often associated with small-cell lung cancer, it can also be testicular cancer and others
- it is most often associated with the presence of anti Hu antibodies

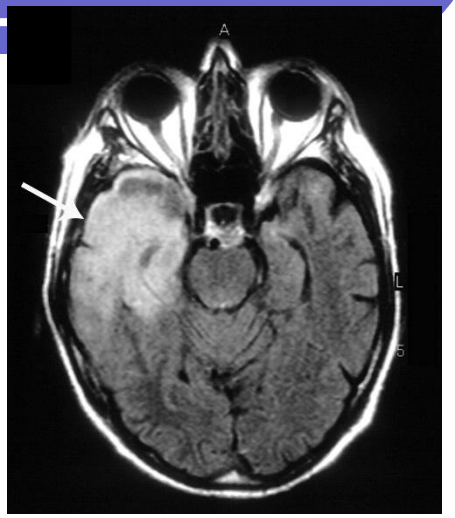
Paraneopalstic encephalomyelitis

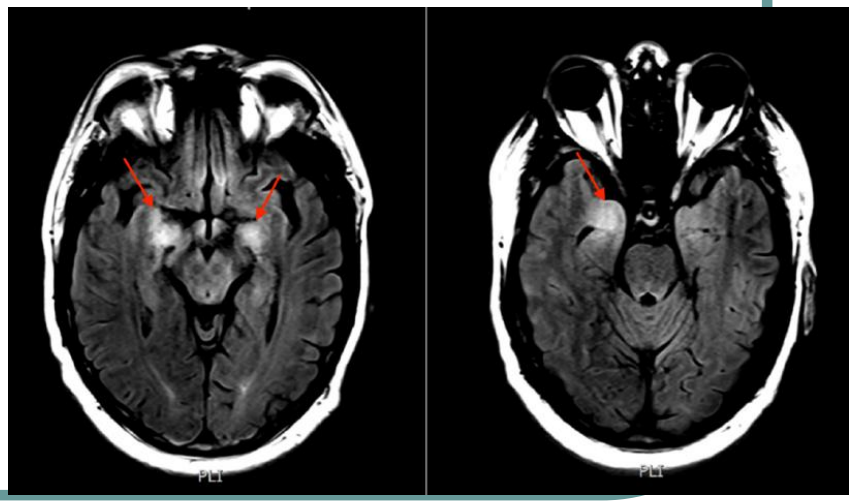
- Diagnostics
- CSF - rule out other diseases
- MR - brain: in MRI T2/FLAIR - mediotemporal hyperintensity
- Search for malignancy - PET CT
- Treatment:
- TU removal or chemotherapy
- High doses of corticoids, plasmapheresis, IVIG, immunosuppressive treatment - azithromycin and rituximab.



Limbic Encephalitis

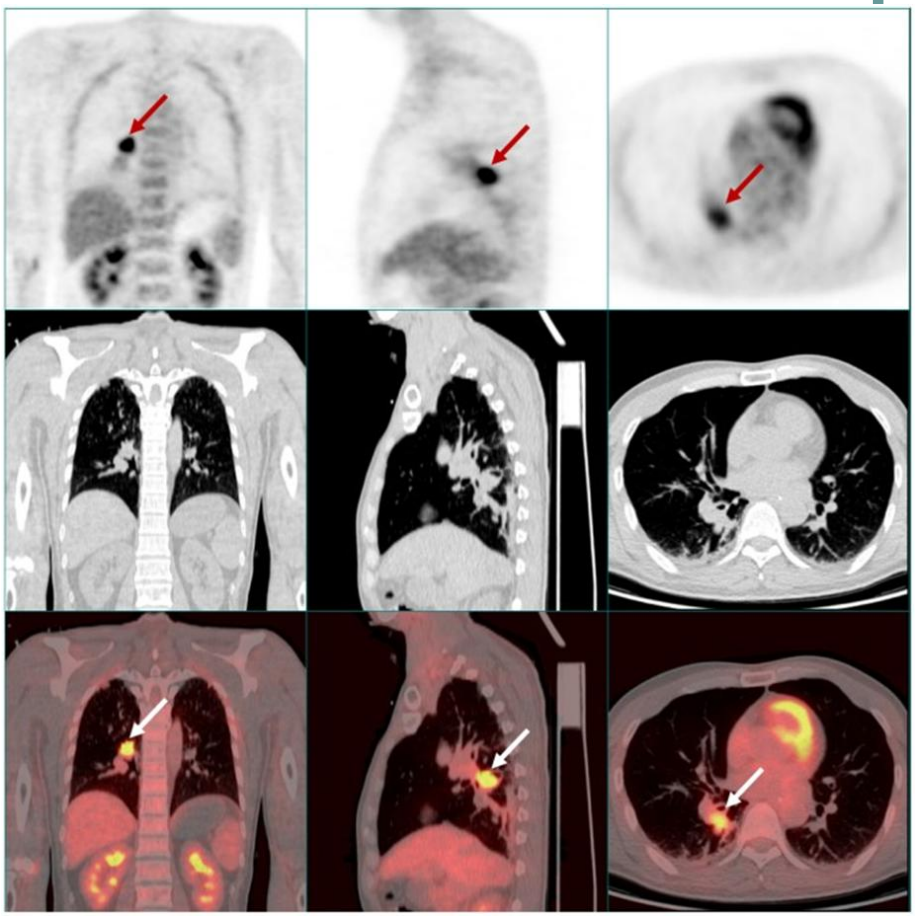
- manifested by rapidly progressive short-term memory impairment, seizures, and psychiatric symptoms within less than 3 months
- it can be paraneoplastic or non-paraneoplastic
- can be associated with the presence of anti AMPAR and GABAbR
- on MRI T2/FLAIR it can be characterized by mediotemporal hyperintensity





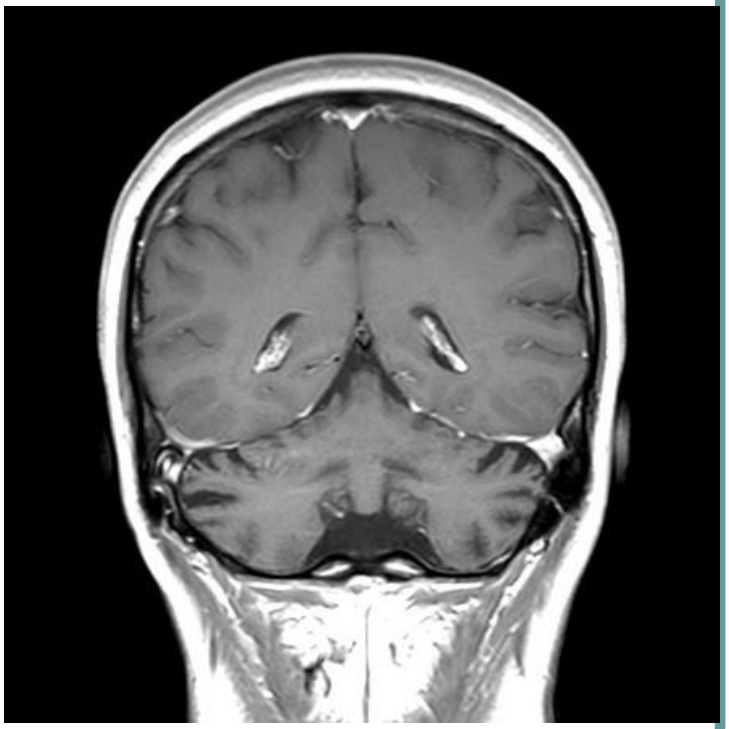
Limbic encefaphalitis

- paraneoplastic is usually associated with small cell lung cancer
- Treatment:
- TU removal or chemotherapy
- High doses of corticoids, plasmapheresis, IVIG, immunosuppressive treatment - azithromycin and rituximab

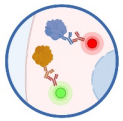
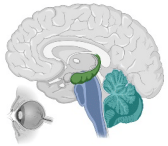
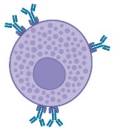
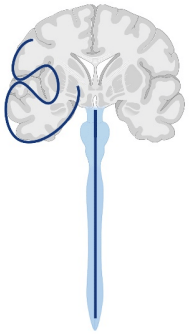


Rapidly Progressive Paraneoplastic Cerebellar Syndrome

- is typically manifested by the rapid development of bilateral cerebellar syndrome limiting daily activities in less than 3 months
- is most often associated with the presence of anti Yo antibodies
- it is usually associated with ovarian and breast malignancy, but also lung or Hodgkin's lymphoma
- Treatment
- Removal of TU, immunosuppressive treatment - small effect



Paraneoplastic syndromes of the central nervous system

Antibody	Cancer risk	Neurological syndrome	Response to immune therapies
Intracellular antibodies (cytoplasmic or nuclear) "High-risk"  **Ho** **Yu** **Ri** **Ma1** **Ma2** T-cell mediated	High risk	 **Rapidly progressive cerebellar syndrome / other cerebellar ataxias** Yo/PCA1; Tr/DNER; KLHL11; PCA2; SOX1; VGCC; DPPX; mGLUR-1  **Opsoclonus-myoclonus syndrome** Yo/PCA1; Hu/ANNA1; Ma1 and Ma2; NMDAR	Poor
Neuronal surface antibodies "Intermediate/low-risk"  **$GABA_BR$** **CASPR2** **GAD65** **DPPX** **LGI1** B-cell mediated	Intermediate risk Low risk	 **Encephalitis/ encephalomyelitis** Hu/ANNA1; Ri/ANNA2; KLHL11; PCA2; Ma1 and Ma2 CV2/CRMP5; $GABA_BR$; AMPAR; CASPR2; NMDAR; LGI1; GFAP **Stiff person syndrome spectrum disorders** Amphiphysin; SOX1; GAD65 DPPX; GlyR	Good

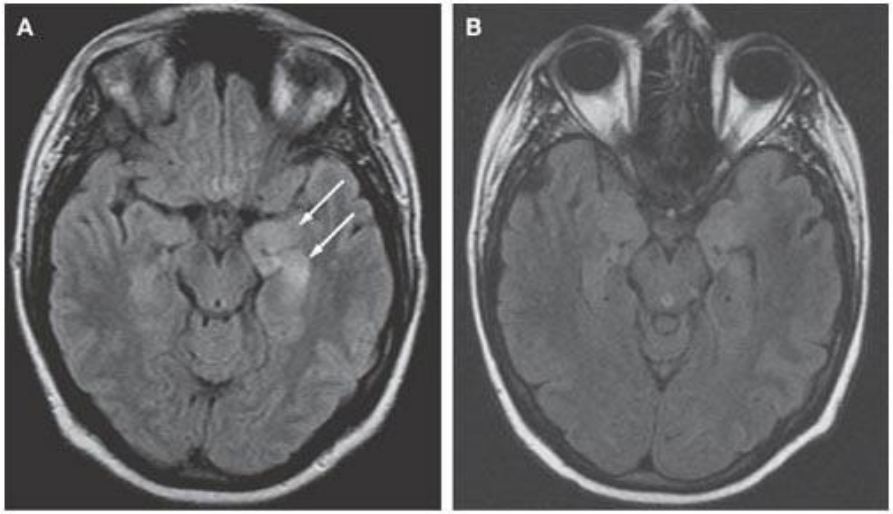
Senzoric paraneoplastic neuronopathy

- Also - dorsal root ganglionitis, characterized by rapidly progressive, asymmetric and often painful sensory symptoms with profound proprioceptive loss affecting the upper limbs more than the lower limbs.
- Paresthesias, anesthesia and pain in the acral parts of the limbs
- It progresses to the trunk and the face area
- Ataxia
- EMG, anti Hu antibodies in serum or cerebrospinal fluid
- Most often associated with small cell carcinoma of the lung, ca of the prostate

anti-NMDAR encefalitis

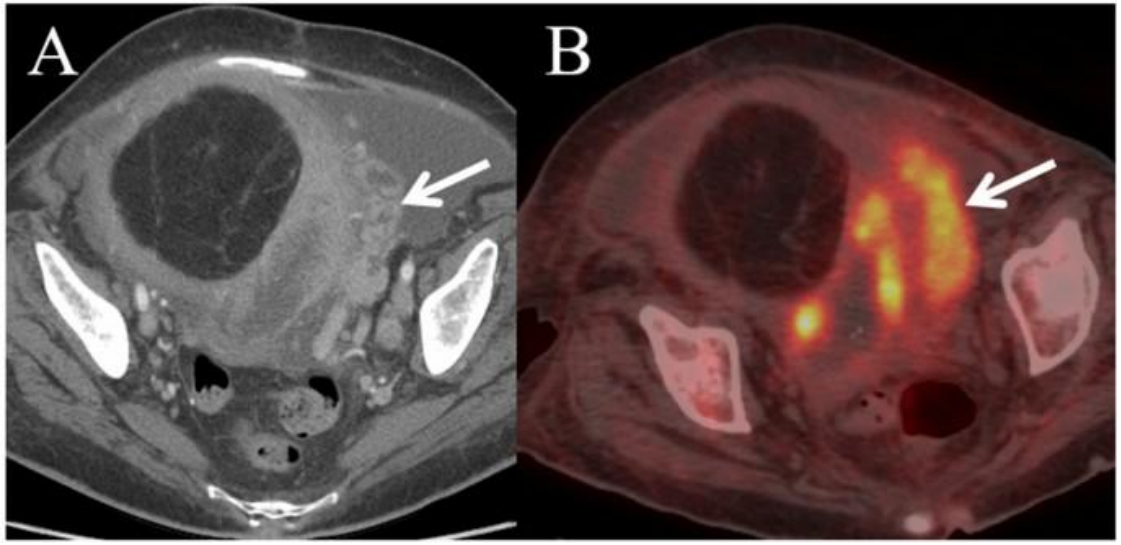
- Anti-NMDA receptor encephalitis is an autoimmune disease in which antibodies attack NMDA (N-methyl-D-aspartate) - a type of glutamate receptor.
- In more than 2/3 of patients are dominated by psychiatric symptoms and may therefore be referred to psychiatry first
- with malignancy it is mostly associated only in older age
- in women aged 18-35, it is often associated with ovarian teratoma
- on MRI T2/FLAIR it can be characterized by mediotemporal hyperintensity
- untreated, it can end fatally

anti-NMDAR encefalitis



Brain MR

PET CT



Lambert – Eatonov myastenic sy

- Similar to myasthenia gravis
- Weakness and fatigue of the patient
- EMG differentiation, serological evidence of distinct antibodies
- Dg of the underlying tumor disease
- Treatment
- Tumor - surgical, RAT, CHT
- Corticoids, cytostatics, IVIG, plasmapheresis

Paraneoplastic syndromes

- All parts of nervous system
  - Central NS
  - Periferal NS
  - Neuromuscular junction
  - Muscles