Brain Tumors (GENERAL)

Last updated: December 22, 2020

EPIDEMIOLOGY

1. CELL OF ORIGIN

2. WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION

3. WHO 2016

4. WHO grades

5. Olsen WHO

6. Neuroepithelial tumors

7. Other CNS tumors

8. CONGENITAL NEOPLASMS

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10. PATHOLOGY

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12. TUMOR LOCATION & TYPES

13. Intraventricular tumors

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17. TUMOR MARKERS / IMMUNOHISTOCHEMISTRY, STAINS

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20. DIAGNOSTIC FEATURES

21. DIAGNOSTIC MODALITIES

22. CLINICAL FEATURES

23. CLINICAL MANIFESTATIONS

24. COMPLICATIONS

25. HYDROCEPHALUS

26. INTRACRANIAL HEMORRHAGE

27. CELL OF ORIGIN

Neoplastic transformation can occur in:

1) Neuroepithelial → most commonly encountered (50-60%) and most feared brain tumors! astrocyte → astrocytoma (incl. glioblastoma multiforme)

2) oligodendrocyte → oligodendroglioma epidermoidocyte → epidermoidoma, epidermoidsblastoma

3) primitive neuroectoderm → medulloblastoma

4) choroid epithelial cell → choroid plexus papilloma / carcinoma

5) arachnoidal fibrilsblasts → meningioma

6) endothelial cell or “stromal” cell → hemangioblastoma

7) primitive notochord remnants → chordoma

8) pituitary cell → adenoma

9) pineal parenchymal cells → pineocytoma

10) Schwann cell → schwannoma (neuroma)

11) primitive lymphocytes → CNS lymphoma

12) primitive germ cells → germ cell, pinealoma, teratoma, cholesteatoma

13) melanocyte → melanotic carcinoma

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WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION

WHO 2016

- CNS tumor diagnoses should consist of a histopathological name followed by the genetic features, with the genetic features following a comma and as adjectives, as in: Diffuse astrocytoma, IDH-mutant and Medulloblastoma, WNT-activated.
- for those entities with more than one genetic determinant, the multiple necessary molecular features are included in the name: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted.
- for a tumor lacking a genetic mutation, the term wildtype can be used if an official "wildtype" entity exists: Glioblastoma, IDH-wildtype. If formal wildtype diagnosis is not available, a tumor lacking a diagnostic mutation is given an NOS designation.

WHO classification of tumours of the central nervous system

<table>
<thead>
<tr>
<th>Tumours of the pineal region</th>
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</thead>
<tbody>
<tr>
<td>Glioblastoma, IDH-wildtype</td>
<td>Ependymoblastoma, IDH-wildtype</td>
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<tr>
<td>Starry sky glioma, IDH-wildtype</td>
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<tr>
<td>Malignant astrocytoma</td>
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<td>Medulloblastoma, NOS</td>
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<tr>
<td>Medulloblastoma, group 4</td>
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<tr>
<td>Medulloblastoma, histologically defined</td>
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Summary of the major changes in the 2016 CNS WHO

1. Formulating concept of how CNS tumor diagnoses are structured in the molecular era

2. Major restructuring of diffuse gliomas, with incorporation of genetically defined entities

3. Major restructuring of medulloblastomas, with incorporation of genetically defined entities

4. Major restructuring of other embryonal tumors, with incorporation of genetically defined entities and removal of the term "primitive neuroectodermal tumor"

5. Incorporation of a genetically defined ependymoma variant

6. Novel approach distinguishing pediatric look-alikes, including designation of novel, genetically defined entity

7. Addition of newly recognized entities, variants and patterns:
   1) IDH-wildtype and IDH-mutant glioblastoma (entities)
   2) Diffuse midline glioma, H3 K27M-mutant (entity)
   3) Embryonal tumor with multilayered rosettes, C19MC-altered (entity)
   4) Ependymoma, RELA fusion-positive (entity)
   5) Diffuse leptomeningeal gliomatosis (entity)
   6) Anaplastic PXA (entity)
   7) Epithelioid glioblastoma (variant)
   8) Glioblastoma with primitive neuronal component (pattern)
   9) Multinodular and vacuolated pattern of ganglion cell tumor (pattern)

8. Deletion of former entities, variants and terms:  
   1) Gliomatosis cerebri
   2) Protoplasmic and fibrillary astrocytoma variants

4) "Primitive neuroectodermal tumor" terminology*

9. Addition of brain invasion as a criterion for atypical meningioma

10. Restructuring of solitary fibrous tumor and hemangiopericytoma (SFT/HPC) as one entity and adapting a grading system to accommodate this change

11. Expansion and clarification of entities included in nerve sheath tumors, with addition of hybrid nerve sheath tumors and separation of melanotic schwannoma from other schwannomas

12. Expansion of entities included in haemangioendothelial tumors of the CNS (lymphomas and histiocytoses)

*no more PNET!
Gliomas are not divided sharply into benign and malignant forms, rather, they represent gradations on spectrum from slowly growing to rapidly growing neoplasms. See p. Onc1 >><br><br>• with time, as more aggressive cells replicate themselves to greater extent than do more indolent cells, gliomas may shift from benign end of spectrum to malignant end (i.e. propensity to transform into higher-grade gloma).<br><br>Quantitative measures of mitotic activity (correlates with malignant clinical behavior):

a) proliferation index - measure of DNA synthesis - uptake of bromodeoxyuridine (thymidine analogue): BrdUrd IV prior to surgery → uptake into nuclei of tumor cells → uptake assessed in biopsy specimens (using BrdUrd-specific antibody).<br><br>b) immunohistochemical staining with antibodies to proliferating cell nuclear antigen (PCNA).<br><br>c) immunohistochemical staining with Ki-67 antibody (recognizes histone protein expressed in proliferating but not quiescent cells).<br><br>Older WHO NEUROEPITHELIAL tumors:

1. Astrocytic tumors:
   1) (juvenile) pilocytic astrocytoma (non-invasive, WHO grade I)
      a) hemispheric
      b) diencephalic
      c) optic
      d) brain stem
      e) cerebellar
   2) subependymal giant cell astrocytoma (non-invasive, WHO grade I)
   3) pleomorphic xanthoastrocytoma (non-invasive, WHO grade I)
   4) astrocytoma (WHO grade II)
      variants: protoplasmic, gemistocytic, fibrillary, mixed
   5) anaplastic (malignant) astrocytoma (WHO grade III)
      a) hemispheric
      b) diencephalic
      c) optic
      d) brain stem
      e) cerebellar
   6) glioblastoma multiforme (WHO grade IV) – most aggressive and most common of all CNS tumors!!!
      variants: giant cell glioblastoma, gliosarcoma

2. Oligodendroglial tumors:
   1) oligodendroglioma (WHO grade II) ≈ 80%
   2) anaplastic (malignant) oligodendroglioma (WHO grade III) ≈ 20%

3. Ependymal cell tumors:
   1) subependymoma (WHO grade I)
   2) ependymoma (WHO grade II)
      variants: cellular, papillary, epithelial, clear cell, mixed
   3) anaplastic ependymoma (WHO grade III)
   4) myxopapillary ependymoma

4. Mixed glioma:
   1) mixed oligoastrocytoma (WHO grade II)
   2) anaplastic (malignant) oligoastrocytoma (WHO grade III)
   3) others (e.g. ependymoastrocytoma)

5. Neuroepithelial tumors of uncertain origin:
   1) polar spongioblastoma (WHO grade IV)
   2) astroblastoma (WHO grade IV)
   3) gliomatosis cerebri (WHO grade IV)

6. Tumors of Choroid Plexus:
   1) choroid plexus papilloma (66-90%)
   2) choroid plexus carcinoma (anaplastic choroid plexus papilloma) (10-33%)

7. Neuroendocrine and mixed neuroendocrine tumors:
   1) gangliocytoma (s. central ganglioneuroma) – neuronal tumor; benign counterpart of neuroblastoma in CNS
   2) dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)
   3) ganglioglioma – gangliocytoma with glial component
   4) anaplastic (malignant) ganglioglioma
   5) desmoplastic infantile ganglioglioma
varies: desmoplastic infantile astrocytoma
6) central neurocytoma – tumor of well-differentiated neurons
7) dyssembryoplastic neuroepithelial tumor (DNET) – benign mixed glial-neuronal tumor
8) olfactory neuroblastoma (esthesioneuroblastoma)
   varies: olfactory neuroepithelioma

8. PINEAL PARENCHYMA tumors
1) pineocytoma (WHO grade I)
2) pineoblastoma (WHO grade IV)
3) pineal parenchymal tumor of intermediate differentiation (WHO grade II-III)
4) papillary tumor of pineal region (WHO grade II-III)

9. Tumors with NEUROBLASTIC or GLIOMATOUS elements (s. EMBRYONAL TUMORS):
1) medulloblastoma
2) primitive neuroectodermal tumors with multipotent differentiation:
   a) medulloblastoma
      varies: melanotic, desmoplastic, medulloblastoma
   b) primitive neuroectodermal tumor (PNET)
3) neuroblastoma
   benign counterparts: ganglioneuroblastoma, ganglioneuroma (s. ganglioma)
4) retinoblastoma
5) ependymoblastoma
6) atypical teratoid/rhabdoid tumor

OTHER/CNS tumors
1. Tumors of SELLAR REGION
   a) pituitary adenoma
   b) pituitary carcinoma
   c) craniopharyngioma

2. HEMATOPOIETIC tumors
   a) primary malignant lymphomas
   b) plasmacytoma
   c) granulocytic sarcoma

3. GERM CELL tumors
   see Intro (various topics) 2.jpg
   a) germ cellomas
   b) embryonal cell carcinoma
   c) yolk sac tumor (endodermal sinus tumor)
   d) choriocarcinoma
   e) teratoma
   f) mixed germ cell tumor

4. Tumors of MENINGES
   a) meningioma
      varies: meningothelial, fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, clear cell, chordoid, lymphoplasmacytic-rich, metastatic subtype
   b) atypical meningioma
   c) anaplastic (malignant) meningioma

5. NON-NEUROTHELLIAL tumors of MENINGES
   a) benign mesenchymal
      a) osteocartilaginous tumors
      b) lipoma
      c) fibrous histiocytoma
   b) malignant mesenchymal
      a) chondrosarcoma
      b) hemangiopericytoma
      c) rhabdomyosarcoma
      d) meningial sarcomatosis
   c) primary melanocytic lesions
      a) diffuse melanosis
      b) melanocytoma
      c) malignant melanoma
      varies: meningial melanomatosis
   d) hemopoietic neoplasms
      a) malignant lymphoma
      b) plasmacytoma
      c) granulocytic sarcoma
e) tumors of uncertain histogenesis - hemangioblastoma (capillary hemangioblastoma)

6. Tumors of CRANIAL /SPINAL NERVES
   a) neurofibroma
   b) schwannoma (neurinoma, neurilemmoma)
      subtypes: cellular, plexiform, melanotic
   c) malignant peripheral nerve sheath tumor
      varies: epithelial, divergent neuroepithelial or epithelial differentiation, melanotic

7. CYSTS and TUMOR-LIKE lesions
   a) Rathke cleft cyst
   b) epidermoid cyst
   c) dermoid cyst
   d) colloid cyst of 3rd ventricle
   e) enterogenous cyst
   f) neuroglial cyst
   g) granular cell tumor (choriocarcinoma, pinocytoma)
   h) hypophalamic neuronal hamartoma
   i) nasal glial heterotopia
   j) plasma cell granuloma

8. LOCAL EXTENSIONS from regional tumors (i.e. secondary intracranial tumors)
BRAIN TUMORS (GENERAL)

1. paraganglioma (chemodectoma)
2. chordoma
3. chondroma
4. chondrosarcoma
5. carcinomas

9. METASTATIC tumors (i.e. secondary intracranial tumors as blood-borne metastases)

10. UNCLASSIFIED tumors

CONGENITAL NEOPLASMS

1. craniopharyngioma
2. chordoma
3. hemangioblastoma
4. choroid cysts
5. germ cell tumors (germinoma, teratoma, etc)
6. dermoid, epidermoid

METASTATIC tumors are ≈5-10 times more common than primary CNS tumors!

– increased longevity of patients with cancer in other systems has resulted in higher incidence of metastatic CNS lesions!
– 15% patients with systemic cancer suffer neurological complications (direct or paraneoplastic).

FREQUENCY

Metastatic tumours are ≈ 5-10 times more common than primary CNS tumors!

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Children (&lt; 14 yrs), %</th>
<th>Adults, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma</td>
<td>20</td>
<td>70-80</td>
</tr>
<tr>
<td>Meningioma</td>
<td>22</td>
<td>10-25</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>4</td>
<td>3-4</td>
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<tr>
<td>Ependymoma</td>
<td>5-10</td>
<td>2-3</td>
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<tr>
<td>Medulloblastoma</td>
<td>21</td>
<td>1.6</td>
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<tr>
<td>Neuroblastoma</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Primary CNS lymphoma</td>
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<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Children (&lt; 2 yrs), %</th>
<th>Adults, %</th>
</tr>
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<tbody>
<tr>
<td>Medulloblastoma</td>
<td>20</td>
<td>1.6</td>
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<tr>
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<td>20</td>
<td>2-7</td>
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<tr>
<td>Low-grade glioma</td>
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Brain tumors (adults) with percentage incidence by category:

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<th>Percentage</th>
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<tr>
<td>Glioblastoma (47)</td>
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<tr>
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<tr>
<td>Anaplastic astrocytoma (24)</td>
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<tr>
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<tr>
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<td>5%</td>
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<tr>
<td>Lymphoma (7)</td>
<td>7%</td>
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<tr>
<td>Other (7)</td>
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</table>

Age-specific incidence of primary CNS tumors by histologic type:

A. Selected histologic types among all age groups.
B. Selected histologic tumor types in children.
In most neoplasms, three zones may be identified:
1) central region of necrosis
2) densely cellular ring (area of CT/MRI contrast enhancement)
3) peripheral edema zone of lesser cellular density (“tumoral infiltration”) with fingers extending peripherally from main mass.

Rosenthal fibers are characteristic feature of:
1) JUVENILE PILOCYTIC ASTROCYTOMAS
2) CRANIOPHARYNGIOMAS
3) ALEXANDER DISEASE (Rosenthal fibers radiate from vessels)
4) around EPENDYMOMAS

Rosenthal fibers in neuropil:
BENIGN vs. MALIGNANT
≈ 1/3 brain tumors can be called BENIGN (mainly extra-axial tumors - meningiomas, acoustic neuromas).

Concept of malignancy in CNS has different meanings from that which applies to systemic cancers;
• term “malignant” has nothing to do with metastasis out of CNS, which is extraordinarily rare.
• term “malignant” describes:
  1) histologic features: BENIGN - grow slowly, low cellularity, few mitoses, no necrosis, no vascular proliferation. MALIGNANT – 1) rapid growth (frequent mitotic figures), 2) invasiveness, 3) vascular proliferation (endothelial hyperplasia), 4) necrosis.
  2) anatomic location - can have lethal consequences irrespective of histologic classification. e.g. benign meningioma, by compressing medulla, can cause cardiorespiratory arrest
  3) possibility of complete surgical removal - unless tumor can be completely excised to last cell, all intracranial neoplasms are potentially malignant in that they may recur, and often do. e.g. gliomas are rarely curable by surgical excision - fundamentally malignant!

Neuroectodermal tumors are never “benign”!

N.B. because cranial vault allows no room for expansion, even BENIGN tumors can be serious! - not clearly separable into BENIGN and MALIGNANT forms.
• e.g. histologically benign PITUITARY ADENOMAS may invade adjacent dura mater and bone and grow into cavernous or sphenoid sinuses.
• e.g. malignant GABAERGIC ASTROCYTOMAS invades brain locally but seldom spreads elsewhere.

Distinction between “benign” and “malignant” is less important than for systemic cancers

Tumor LOCATION & TYPES

ADULTS - most commonly (70%) above tentorium; most common tumors above tentorium (extra-axial tumors predominate) – gliomas and metastases; meningiomas.
most common tumors below tentorium (extra-axial tumors predominate) – neurectodermal and hemangioblastomas.

CHILDREN (2-12 yrs) - most commonly (70%) below tentorium (posterior cranial fossa, often in midline): medulloblastomas, cerebellar astrocytomas, ependymomas, brain stem or optic nerve gliomas, germinomas, congenital tumors.

ADOLESCENTS (>12 yrs) and INFANTS (<2 yrs) - equal frequencies below tentorium and above tentorium.

• distribution of parenchymal tumors is directly related to mass of lobe or region.

PATHOLOGY
Age | Hemispheres | Diencephalon | Posterior Fossa | Meninges | Spinal Cord
---|-------------|-------------|---------------|-----------|-----------
Adulthood | Astrocytoma, oligodendroglioma, metastasis, lymphoma | Astrocytoma, colloid cyst, primary adenoma | Metastases, hemangioendothelioma | Metastoma, CNS, schwannoma, metastases, lymphoma | Metastoma, nerve sheath tumors, astrocytoma, epidermoid
Childhood | Astrocytoma, ependymoma, choroid plexus, primitive neuroectodermal tumor | Germ cell tumors, stromatolympoma | Medulloblastoma*, ependymoma, central plasminc astrocytoma, brain stem astrocytoma, choroid plexus tumor | Leukemia, lymphoma | Nerve sheath tumors, astrocytoma

**INTRAVENTRICULAR TUMORS**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Typical site</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COLLOID CYST</strong></td>
<td>Foramen of Monro / 3rd ventricle</td>
</tr>
<tr>
<td><strong>SEGA</strong></td>
<td>Foramen of Monro</td>
</tr>
<tr>
<td><strong>MENINGIOMA</strong></td>
<td>Trigone of lateral ventricle</td>
</tr>
<tr>
<td><strong>CHOROID PLEXUS PAPILLOMA</strong></td>
<td>4th ventricle</td>
</tr>
<tr>
<td><strong>EPENDYMOMA</strong></td>
<td>Lateral ventricle (more common in children), 4th ventricle</td>
</tr>
<tr>
<td><strong>SCHIOPEXICOMA</strong></td>
<td>Lateral ventricle, 4th ventricle</td>
</tr>
<tr>
<td><strong>NEUROCYTOMA</strong></td>
<td>Lateral ventricles (involving septum pellucidum)</td>
</tr>
<tr>
<td><strong>METASTASES</strong></td>
<td>Lateral ventricles, ependyma and choroid plexus</td>
</tr>
</tbody>
</table>

* Different: Neurocyticercosis

**Tumor SPREAD**

Tumors **ordinarily grow focally within one area** (but nevertheless they cannot be cured surgically):

1. intact BBB
2. brain lacks lymphatics
   - even slow-growing gliomas can widely infiltrate brain.
   - glioma cells spread preferentially along white matter tracts (may cross corpus callosum into contralateral hemisphere) - brain function may be long preserved!

-Some types may spread via CSF through ventricular / subarachnoid spaces:
- HIGH-GRADE GLIOMAS (10-25%)
- PRIMITIVE NEUROECTODERMAL TUMORS, incl. MEDULLOBLASTOMAS (10-20%)
- Ependymomas (11%)
- CHOROID PLEXUS CARCINOMAS (1%)
- PINEAL GERMINOMAS (rare).

- spread down ventriculoperitoneal shunt – intra-abdominal metastases.

Metastasis out of cranial cavity / spinal canal is extraordinarily rare (< 1%) even for most malignant gliomas (unless operative procedure has interfered with normal meningeal barriers).

**Tumor BURDEN**

- tumor mass of 30-60 g (3.6 x 10^10 cells) usually produces neurologic symptoms.
- brain cancer is lethal when tumor and its associated edema reaches 100 g (vs. 1000 g in systemic cancers)
- immune system per se can suppress and eventually kill only 0.0001 g, or 1 x 10^5 glioma cells.
parental cell population is genetically unstable → tumors are heterogeneous in cellular content:
a) genetic (includ. chromosomal content [ranges from near diploid to hypo- or hypertetraploid] and molecular aberrations).
b) phenotypic (cells that are immediately adjacent to one another may have very different histochemical appearance).

REGIONAL DIFFERENCES develop when tumors begin to invade surrounding normal brain - during migration, some cells develop additional abnormalities that confer selective advantage for growth → tumor is seeded with microfoci that are both genotypically and phenotypically different.

TUMOR MARKERS / IMMUNOHISTOCHEMISTRY, STAINS

- ATRX (alpha-thalassemia/mental retardation syndrome X-linked) gene
  - ATRX is present in every cell!
  - Loss of ATRX = astrocytic lineage (grade II/III astrocytomas and secondary GBM)

- Brachyury (protein encoded by the TbxXT gene, transcription factor within the T-box family of genes)
  - Early mutational event in astrocytoma evolution (discriminates chondroma from chondrosarcoma).
  - Present in many tumors (e.g. hemangioblastomas) helps to differentiate from clear cell renal cell carcinoma metastases in von Hippel-Lindau syndrome.

- CD68 (protein highly expressed by cells in the monocyte lineage: macrophagia, histiocytes) → differentiates histiocytes from lymphoma.

CD4 - T-cell lymphoma.

- Drosinum – tumors containing muscle (schlomomysarcoma, teratoma, etc.), primitive neuroectodermal tumor.

- EGFR (epidermal-derived growth factor receptor) → aberrantly expressed (usually amplified*) in many gliomas.
  - "poor prognostic factor!"

- EMA (epithelial membrane antigen) – epithelia marker (endymymoma, meningioma, epithelial areas of teratomas, chbroid tumors)
  - N.B. not present in melanoma!

- GEAP (gliarial fibrillary acidic protein) – expressed in astrocytes (it is a type III intermediate filament (IF) protein important for cytoskeleton), marker for gliob tumors, e.g. unaplastic astrocytoma:

- Luxol fast blue dye - myelin fibers appear blue, neuropil appears pink, and nerve cells appear purple.

- Neuro-specific enolase - questional utility → positive in normal and neoplastic cells of neural and non-neural origin.

- p53 mutation – astrocytic tumors (vs. oligo*)
  - In Fragmenzi syndrome (inherited p53 mutation) → strong predisposition to astrocytoma!
  - p53 mutation goes "hand to hand" with IDH mutation.
  - Glial attenuates that show p53 mutation are termed secondary glioblastomas (type 1) occur in younger patients whose tumors have progressed from lower grade astrocytoma.

- Placental alkaline phosphatase – germ cell tumors

- Retinal S-antigen – pineal parenchymal tumors, primitive neuroectodermal tumors, retinoblastoma.

- S-100 – present in cells derived from the neural crest (Schwann cells, and melanocytes) - markers for certain melanomas, schwannomas (100%), neurofibromas (weaker than schwannomas), malignant peripheral nerve sheath tumors (50%, may be weak and/or focal).

- SSTR2 (somatostatin receptor type 2)
  - Most sensitive marker for meningiomas (present in 100%).

- STAT5 – hemangiopericytoma.

- Synaptophysin –integral membrane protein localized to synaptic vesicles (specific and sensitive marker for synaptic terminals), gliosaronal tumors (primitive neuroectodermal tumor, ganglioglioma, gangliocytoma, central neurocytoma, neuroendocrine tumors)
  - Diagnostically, it is often used in combination with chromogranin A.

- Vascular proliferation:
  - a) astrocytic lineage = GBM (grade IV)

While tumors are monoclonal in origin (i.e. they originate from single cell),

as they grow they progress through series of genomic changes that permit evolution to more and more malignant stages.
**ETIOLOGY, RISK FACTORS**

**SEIZURES**

Seizures may herald development of cerebral tumors by several years!
- British study (Journal of Neurology, Neurosurgery and Psychiatry, online March 28, 2011):— risk for any cerebral tumor after first admission for epilepsy is increased 20-fold (risk for malignant tumors is more than twice that for benign tumors).
— risk is still elevated several years after first admission for epilepsy → need for continued surveillance of patients with new-onset seizures.

**ENVIRONMENTAL EXPOSURE**

Numerous epidemiologic studies* suggest statistically significant increased incidence of astrocytomas in people exposed to petrochemicals (e.g. in rubber industry) or electromagnetic radiation.
- equally impressive studies, however, have not confirmed association.
- well-documented environmental risk factor (Israeli study) - ionizing radiation (e.g. given for treatment of tinea capitis) - increases risk for meningiomas almost 10 times and for gliomas 2.5 times.
- insufficient epidemiologic evidence to support or refute claims, that hand-held cellular telephones generate electromagnetic radiation and cause brain tumors.
- both RNA and DNA viruses can induce animal brain tumors, but few viruses have been found to account for specific human tumor (e.g. Epstein-Barr virus evidence in primary CNS lymphoma tissue).
- immunosuppression (transplant recipients, AIDS patients, Wiskott-Aldrich syndrome, ataxia-telangiectasia) substantially increases risks for primary CNS lymphomas but not gliomas.
- role of trauma is unproven.

The only proven environmental risk factor for brain tumor is previous exposure to high-dose ionizing radiation

**TUMORIGENESIS**

- multistep process (probably at least 4-6 separate steps - multiple local mutations and clonal expansion).

Most important genetic markers - see above >>

**Proto-oncogenes**

Proto-oncogenes mutated / overexpressed in brain tumors:
1) *EGFR* (erb-B) - encodes epidermal-derived growth factor receptor; aberrantly expressed (usually amplified) in many gliomas!
2) *c-sis* - encodes platelet-derived growth factor
3) *c-myc*
4) *ras*
5) *H-ras*
6) *gli*
- medulloblastomas, 50% glioblastomas have homogeneously staining regions and double minute chromosomes - may contain amplified proto-oncogenes.
**TUMOR SUPPRESSOR GENES**

Tumor suppressor genes associated with nervous system tumors

- **p53**: Tumor suppressor gene
- **HEREDITARY SYNDROMES**
  - Neurofibromatosis (von Recklinghausen's disease)
  - Li-Fraumeni syndrome
  - NF1 (17q11.2), NF2 (22q11.2)
- **HEREDITARY SYNDROMES associated with brain tumors**
- **HEREDITARY SYNDROMES associated with breast cancer**

**GROWTH FACTORS**

- have potent growth stimulatory effects on glioma cells in culture:
  1. platelet-derived growth factor (PDGF)
  2. epidermal-derived growth factor (EGF)
  3. transforming growth factor-α (TGF-α) - 50% homology with EGF, secreted by numerous tumors (incl. high-grade malignant gliomas).
  4. fibroblast growth factor (FGF).
- many glioma cells produce growth factors and express appropriate growth factor receptor on their surface membranes - constantly stimulate own growth and division (AUTOCRINE/GROWTH).
- N.B. normal brain cells are genetically quiescent (neurons are incapable of division after birth; glial cells are minimally proliferative in reactive or regenerative gliosis).
- **cardinal histopathologic features that define malignant glioma -**
  - cellular atypia, cellularity, mitoses, endothelial hyperplasia, necrosis.
  - - all (with exception of necrosis - attributed to growth beyond capacity of blood supply) are subject to modulation by growth factors.
- > 60% gliomas have **telomerase activity** (correlates with tumor grading, lowest in grade tumors).

**HEREDITARY SYNDROMES associated with brain tumors** - make only < 5% of all primary CNS tumors cases:

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Nervous Tumor</th>
<th>Other tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofibromatosis type 1</td>
<td>NF1 (17p11)</td>
<td>Neurofibroma, malignant peripheral nerve sheath tumor (MPNST), meningioma, optic nerve glioma, (low-grade astrocytoma)</td>
<td>Iris hamartomas, oculoskeletal lesions, phaeochromocytoma, leukemia</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>NF2 (22q11)</td>
<td>Bilateral vertebral/retinoblastoma, peripheral schwannoma, meningioma, astrocytoma, meningiogliomatosis, spinal ependymoma, glial hamartias, cerebral calcification</td>
<td>Retinal hamartoma, breast carcinoma, cutaneous angiofibroma, subungual fibroma</td>
</tr>
<tr>
<td>von Hippel-Lindau syndrome</td>
<td>VHL (3p25)</td>
<td>Hemangioblastoma</td>
<td>Retinal hemangioblastoma, renal cell carcinoma, phaeochromocytoma, visceral cysts</td>
</tr>
<tr>
<td>Tuberous sclerosis complex 1</td>
<td>TSC1 (9q34), TSC2 (16p13)</td>
<td>Subependymal giant cell astrocytoma (SEGAs), cortical tubers, bilateral subependymal gangliocytomas and subependymal hamartomas</td>
<td>Pulmonary hypertension, adenomatous polyps of small intestine, cysts of lung and kidney, renal angiomylipoma, lymphangioleiomyomatosis, cutaneous angiofibroma, subungual fibroma</td>
</tr>
<tr>
<td>Tuberous sclerosis complex 2</td>
<td>NF3 (17p13)</td>
<td>Various malignant gliomas, INI1 (medulloblastoma)</td>
<td>Breast carcinoma, bone and soft tissue sarcoma, adrenocortical carcinoma, leukemias</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia 1</td>
<td>not known</td>
<td>Pituitary adenomas, <em>malignant</em> schwannomas</td>
<td>Retinal hemangioblastoma, renal cell carcinoma, phaeochromocytoma, visceral cysts</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>RB1 (13q14)</td>
<td>Retinoblastoma, pineoblastoma</td>
<td>Retinal hemangioblastoma, renal cell carcinoma, phaeochromocytoma, visceral cysts</td>
</tr>
<tr>
<td>Tuberous sclerosis complex 1</td>
<td>APC, TSC1</td>
<td>Colon polyps</td>
<td>Retinal hemangioblastoma, renal cell carcinoma, phaeochromocytoma, visceral cysts</td>
</tr>
<tr>
<td>Tuberous sclerosis complex 2</td>
<td>BMP, medulloblastoma</td>
<td></td>
<td>Retinal hemangioblastoma, renal cell carcinoma, phaeochromocytoma, visceral cysts</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>WRN (10q23)</td>
<td>Meningioma</td>
<td>Retinal hemangioblastoma, renal cell carcinoma, phaeochromocytoma, visceral cysts</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td><em>Pten</em> (10q23)</td>
<td>Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos), megalencephaly</td>
<td>Hamartomas of skin. Of tract, gingival fibromatosis, multiple telangiectasias, thymic neoplasms, breast carcinoma</td>
</tr>
<tr>
<td>Gorlin syndrome (nevoid basal cell carcinoma syndrome)</td>
<td>SMH2, MLH1, MSH2, MSH6, MLH1, MSH2, PMS2, PMS3</td>
<td>Medulloblastoma (in &gt; 95% mutation carriers)</td>
<td>Autosomal dominant nevoid basilar cell carcinoma, jaw keratocysts, skeletal abnormalities, ovarian fibromas, esophageal calciifications, palmar and plantar pits</td>
</tr>
<tr>
<td>Muir-Torre syndrome</td>
<td>SMH2, MLH1 - DNA monochip repair genes (subtype of Lynch Type II hereditary nonpolyposis colon cancer (HNPCC))</td>
<td></td>
<td>Autosomal dominant nevoid basilar cell carcinoma, jaw keratocysts, skeletal abnormalities, ovarian fibromas, esophageal calciifications, palmar and plantar pits</td>
</tr>
<tr>
<td>Cowden syndrome (neurofibromatosis type 2)</td>
<td><em>Phaeochromocytoma</em></td>
<td><em>Lentigines</em></td>
<td><strong>Human analog of patched gene of Drosophila</strong></td>
</tr>
<tr>
<td>Rubinstein-Taybi syndrome</td>
<td>INI1 (22q11.2)</td>
<td>A/RTF</td>
<td>Bilateral renal malformations, malformations of corpus callsum</td>
</tr>
</tbody>
</table>
Most common scenario - patient inherits one mutant (inactivating) copy of tumor-suppressor gene and thus carries so-called germline mutation in every cell, which is unvediled when second copy of tumor-suppressor gene is inactivated (either by mutation or by loss of portion of chromosome).

**PATHOPHYSIOLOGY**

**BBB, BLOOD FLOW & BRAIN EDEMA**

BBB is substantially altered (tight endothelial cell junctions are disrupted, fenestrations appear within endothelium, and pinocytotic vesicles increase), but is not completely broken in brain tumor.

- *water-soluble, ionized molecules, macromolecules can enter tumor.*
- *entry of some water-soluble chemotherapeutic agents is still impeded.*

Tumor blood flow is about same as in tumor-free white matter.

**Causes of brain edema:**

1. Disrupted BBB
2. Leaky capillaries (permeability varies over range of 1 to 100 times normal brain values)

Brain edema type in tumors is **vasogenic**

N.B. brain tumor increases capillary permeability not only in tumor itself, but also in adjacent capillaries (probably through action of soluble "vascular permeability factor"), and in other regions as well. Thus, it was thought that edema in adjacent white matter is result of diffusion of fluid from tumor.

- *vascular endothelial growth factor (VEGF)*
- *enormous edema surrounding small neoplasm suggests rapidly growing malignant tumor (exception – meningioma - benign slow-growing tumor that can produce profound edema and contrast enhancement).*

*it is unusual for 20 y tumor to produce 100 ml mass because of associated edema.*

**PATHOPHYSIOLOGY of CLINICAL FEATURES**

**Intra-axial tumors** produce symptoms by three mechanisms:

A. Tumor cells infiltrate among nerve cells and along nerve fiber tracts, producing little or no damage to these structures (low-grade astrocytoma, oligodendroglioma) - first manifestation is often single seizure
B. Tumor cells grow as mass, displacing surrounding brain tissue, but not destroying it (metastatic brain tumors) → generalized and focal symptoms, which return to normal if tumor can be resected.
C. Tumor cells infiltrate, grow, as mass, and destroy surrounding neuritopl (malignant glioma) → generalized and focal symptoms, which do not improve after treatment.

**Extra-axial tumors** compress adjacent brain - may present only as mass (without focal symptoms), or may induce seizure focus; tumor resection often restores patient to normal neurologic state.

- *as tumor grows, signs of brain damage become evident.*

How intracranial neoplasms increase ICP

1) Tumor mass
2) Cerebral edema adjacent to neoplasm
3) Obstruction of CSF pathways (producing hydrocephalus):
   - Intraventricular (at Monro foramen, aqueduct, 4th ventricle)
   - Leukemic or carcinomatous involvement of meninges
   - Obstruction of venous pathways

- *75% infants < 6 months of age have tumor volumes > 1/3 of their intracranial volume*

**CLINICAL FEATURES**

Characteristic feature of all intracranial neoplasms is that they produce *progressive* symptoms!

Clinical presentation depends primarily on:

1. Age of patient (ability of skull bones to adjust to growing intracranial mass).
2. Neurological symptoms due to neoplasm itself (producing hydrocephalus)
3. Obstruction of CSF pathways (producing hydrocephalus): intraventricular (at Monro foramen, aqueduct, 4th ventricle), leukenic or carcinomatous involvement of meninges, obstruction of venous pathways.

- *75% infants < 6 months of age have tumor volumes > 1/3 of their intracranial volume - plasticity of cranial vault allows asymptomatic growth.*

**Asymptomatic cases:**

1) Silent areas (tumors may grow large): parietal or frontal association cortices, neodominant temporal lobe
2) Slow growth (brain can accommodate to slowly growing mass).

**Manifestations can be divided** (but it may not be possible to differentiate these except in retrospect):

a) **Focal symptoms due to tumor itself** (direct compression or infiltration)
   - Generalized symptoms due to secondary consequences (mass effect causing ICP) – tumor volume, peritumoral edema, hydrocephalus, shift of critical structures.
   - *these may cause false-localizing signs!*

Systemic symptoms (malaise, weight loss, anorexia, fever) suggests metastatic rather than primary brain tumor!

**KARNOFSKY performance scale:** objective measurement of functional ability (used in assessing and following patients with CNS neoplasm):

- 100 – Normal (no evidence of disease)
- 90 – Minor symptoms (able to carry on normal activity)
- 80 – Some symptoms (normal activity with effort)
- 70 – Unable to carry on normal activity (cares for self) – level of function justifying aggressive therapy!
- 60 – Cares for most needs (requires occasional assistance)
- 50 – Requires considerable assistance
- 40 – Disabled
- 30 – Severely disabled

**SYMPTOMS**

- Focal symptoms (result of localizing lesion):
  - *Seizure (epilepsy)*
  - *Focal neurological deficit (paralysis, sensory loss)*
  - *Cranial nerve palsy (tumor compresses brain stem or cranial nerve)*

- Generalized symptoms (result of increased ICP):
  - *Cerebral edema (intracranial mass)*
  - *Brain stem compression (vascular collapse, respiratory arrest)*

- **Vasogenic edema**
  - *Increased CSF pressure (hydrocephalus)*

- **Obstructive hydrocephalus**
  - *Increased CSF pressure (hydrocephalus)*
  - *Ventricular enlargement (obstruction of CSF pathways)*

- **Primary headache**
  - *Occipital headache, temporal headache*

- **Posterior fossa tumors**
  - *Abnormal nystagmus (lateral, vertical)*

- **Primary headache**
  - *Occipital headache, temporal headache*

- **Posterior fossa tumors**
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- **Posterior fossa tumors**
  - *Abnormal nystagmus (lateral, vertical)*

- **Primary headache**
  - *Occipital headache, temporal headache*
Brain tumors usually present with one of three syndromes:

- a) nonlocal neurologic disorder (due to ICP)
- b) subacute progression of focal neurologic deficit (rarely stroke-like onset)
- c) seizure

ICP

1. Headache – chief complaint in 30% patients (most common in large tumors with midline shift):
   - with most brain tumors, headache is relatively late sequel; occurs in 50-60% primary brain tumors;
   - rare as initial symptom in brainstem tumors, cerebellopontine angle tumors, pituitary tumors, craniohypophyseal.
   - about features of “classic” brain tumor headache ➔ see p. S50 >>
   - typically semilocalized in vicinity of tumor (e.g. worse on side of tumor); posterior fossa tumors may present with pain referred to occipital region.
   - with time, plateau waves of increased ICP are replaced with sustained elevated ICP - headache gradually increases in intensity or duration ➔ becomes so unrelenting that patient seeks medical attention.

Significant overlap between brain tumor headache and migraine or tension-type headache.

No pattern is diagnostic of brain tumor.

1. Intense paroxysmal headaches may develop abruptly (within seconds); last only a few minutes and terminate as quickly as they come.
   - ominous sign of markedly increased ICP (ICP monitoring shows that peak pressure coincides with plateau waves).
   - during episode, patient may vomit, lose vision, consciousness, fall.
   - possible mechanism - acute hydrocephalus (bulb valve obstruction of CSF outflow with tumor in ventricular system).

2. Vomiting
   - associated with nausea and headache.
   - direct compression of vomiting center ➔ projectile vomiting - highly characteristic of posterior fossa tumors.
   - N.B. “projectile” is misnomer - nothing pathognomonic about forcefulness of ejection; term “projectile” more appropriately refers to vomiting without antecedent nausea or headache (precedes appearance of headache by weeks).

3. Deterioration in mental status (psychomotor retardation, sleep / cognitive / social disturbances, confusion, lethargy) ➔ see p. S50 >>
   - frequent clinical manifestation of intracranial tumor!
   - often subtle in presentation and onset and may not attract attention of friends and family members until patient begins to behave unusually.
   - N.B. it is not unusual for patient to seek psychiatric help (up to 20% of all patients)

4. Cushing reflex signals life-threatening ICP ↑↑↑
   ➔ see p. S50 >>

5. Brain mass shifts (may manifest as false-localizing signs) - CN6 palsy, CN3 palsy, ipsilateral hemiparesis (compression of opposite cerebral peduncle against Kernohan’s notch), ipsilateral visual field defects (compression of opposite PCA), nuchal rigidity & torticollis (herniation of cerebellar tonsils), etc.

*torticollis also may be due to CN4 palsy


SYMPTOMS due to TUMOR ITSELF (FOCAL BRAIN DYSFUNCTION)

- may be absent in tumors growing in silent areas.
- result from compression of neurons and white matter tracts by expanding tumor and accompanying edema.
- vascular compression may produce focal brain ischemia.

1. Seizures – occur in 20-75% patients (as presenting symptom in 18-50% cases);
   - focal or generalized
   - most common with GROWING tumors affecting cortex (esp. meningiomas, oligodendrogliomas, low-grade gliomas).
   - Even small meningiomas that compress adjacent cerebral cortex may present with seizures!
   - Epilepsy rates range 60-100% in low-grade gliomas and 25-60% in high-grade gliomas.
   - suggestive features: status epilepticus at onset, prolonged postictal paralysis*, resistance to medical control, focal symptoms.

- brain tumor patients have higher incidence of postictal neurologic deficit!

2. Negative signs
e - hemiparesis, sensory loss, aphasia, cranial nerve palsies, visual deficits, hearing impairment, ataxia, personality changes, etc.
- multiple meningeal or diffuse brain infiltration (by glioma or lymphoma) may present as dementia or decline in level of alertness.
- hand preference in child < 3-5 yrs may signify hemiparesis.

3. Hyperactive function
   - primary / partial tumors ➔ hormone overproduction.
   - choroid plexus papilloma ➔ CSF overproduction.

WHO performance scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self care, but unable to carry out any work activity. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry out any self care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

In series of 111 patients, headache had characteristics similar to migraine in 9% and to tension-type headache in 77%, while “classic” brain tumor headache occurred in only 17%.

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**REGIONAL FEATURES**

**SUPRATENTORIAL TUMORS**

- progressive focal neurologic signs and seizures predominate.

**Frontal lobe**

1. Seizures - may preceed other symptoms by months or years.
2. Intellectual impairment (esp. with bilateral tumors, e.g. butterfly glioma)
4. Personality changes: see also: P. Psy 5
   a) disorientational prefrontal lesions → apathetic & indifferent (pseudodementia)  
   b) orbital prefrontal lesions → loss of inhibition & euphoric (pseudopsychopathic).
7. Anoma (e.g. meningioma of olfactory groove).

**Temporal lobe**

1. Personality change (bizarre thinking, trance-like states, mood symptoms, immature emotional behavior; bilateral amygdaloid lesions → Klöver-Bucy syndrome)  
2. Sensory aphasia, anoma.
4. Contralateral hemianopia (or superior quadrantanopia).
5. Impairment of recent memory (bilateral hippocampal lesions → Korsakoff amnesia)

   N.B. temporal tumors (esp. in nondominant hemisphere) are often relatively "silent"!

**Parietal lobe**

1. Seizures - generalized or sensory focal seizures.
2. Impaired contralateral cortical sensory modalities (position sense, two-point discrimination, stereognosis).
3. Contralateral homonymous hemianopia (or inferior quadrantanopia).
5. Dominant hemisphere - Gerstmann’s syndrome (agraphia, acalculia, finger agnosia).

**Occipital lobe**

- contralateral quadrantanopia or hemianopia with sparing of macula; visual misperceptions & hallucinations; bilateral lesions – cortical blindness.

**Thalamus**

1. Hydrocephalus.
2. Contralateral sensory abnormality, neuropathic pain, intermittent parasthesias.
3. Involvement of basal ganglia → contralateral intention tremor, hemiballistic movement.
4. Involvement of hypothalamus → eating disorders, precocious puberty.

**POSTERIOR FOCUS**

More devastating than supraventricular tumors (limited space + vital brain stem nuclei)  
1) early CSF flow obstruction → hydrocephalus (rapidly worsening mental status)  
2) projectile vomiting  
3) common symptoms – cranial nerve dysfunction (CN6, CN7), nystagmus, ataxia, long tract signs.

- commonest tumor of brain stem is astrocytoma.

**DIAGNOSIS**

**BLOOD TESTS**

Primary brain tumors typically do not produce blood abnormalities (anemia, ESR↑) or tumor-specific antigens.

- polysystemia associated with cerebellar tumor - presumptive evidence of MENINGIOMAS.

Tumor Markers - see above >>

With MRI ability to image tumors clearly, role of tumor markers is more limited than in other parts of body!

**URINE TESTS**

Two markers in urine can be effective, noninvasive way of detecting presence / recurrence of brain tumors:

1) matrix metalloproteinase-2 (MMP-2)  
2) vascular endothelial growth factor (VEGF) - both are secreted by tumor tissue (have role in tumor angiogenesis).

**OPTICHEMOSTOSCOPY**

1. Papilledema - most reliable sign of ICP↑ (but present in only = 20% patients) see p. Ey62 >>
   - more common with tumors that occlude CSF ways → infratentorial, pineal, thalamic, 3rd ventricle tumors.
2. Other signs of ICP↑ see p. SJ5 >>

- thorough ophthalmologic examination (incl. visual field testing) is important in pre- and postoperative evaluation of tumors adjacent to visual / oculomotor pathways.

**SKULL X-RAY**

- only rare indications:  
  1) screening skull for metastatic disease  
  2) assessing integrity of various shunts  
  - may show signs of raised ICP. see p. SJ5 >>
  - tumor calcification.
  - MENINGIOMAS: hyperostotic bone reaction, enlargement of middle meningeal artery grooves.
  - DERMATOMYOSITIS, SCHWANNOMAS: bone thinning → enlargement of middle cranial fossa or internal auditory meatus.

**PNEUMOENCEPHALOGRAPHY**

- historical method for diagnosing brain tumors.
cerebral (audiometry, auditory evoked potential testing, electronystagmography)

NEUROIMAGING

MRI
CT

Indications - diagnosing:
1) neoplastic meningitis (malignant cells in CSF) – LP indicated only if:
   a) symptoms suggest meningeal involvement,
   b) parenchymal tumor has propensity to seed (e.g. MEDULLOBLASTOMA, EPENDYMOMA, CHOROID PLEXUS CARCINOMA, some EMBRYONAL PNEUMATIZED SUPRASELLAR TUMORS) – combine with spinal MRI (CSF is negative in ~ 50% MRI-positive cases)!

N.B. routine CSF examination in all patients with tumors, searching for malignant cells, is discouraged.

2) benign intracranial hypertension (pseudotumor cerebri)

N.B. both conditions are not emergency, wait until tumor (if present) has been brought under control by surgical decompression, corticosteroids, radiation, or chemotherapy.

e.g. LP is safe about 10-21 days after intracranial decompression.

NEUROIMAGING

- indispensable component of modern diagnosis - confirms presence, but not type, of brain tumor!
- secure focus or slow wave focus over hemisphere tumor
- generalized slowing suggests either involvement of deep midline centers or metabolic problems.
- unresponsive patient often requires EEG to rule out subclinical seizures.

CT WITH CONTRAST

- faster (between screening examination (but MRI is test of choice!)

- better definition (than MRI) of calcification – suggests more indolent growth;
- tumors that tend to calcify: oligodendrogliomas (90%), meningiomas, craniopharyngioma, teratoma, chordoma, chordoid plexus tumors, ependymoma, central neurocytoma.
- CT preferable (over MRI) for evaluating bones, intratumoral hemorrage.
- CT-guided localization (in stereotactic biopsies) is more precise than MRI (because of “MRI artifact”).
- on enhanced CT – most commonly as ring-like hyperdense region around central radiolucent area.
- enhanced CT can be completely normal (± subtle mass effect).
- on nonenhanced CT

- tumors can be hypo-, iso- or hyperdense (depends on histological tumor type and presence of calcification or necrosis) relative to surrounding structures.
- associated vasogenic edema (low attenuation in white matter).
- contrast enhancement is sign of malignancy / high-grade! (exceptions exist)

- Pituitary adenomas always enhance less than normal pituitary gland!

Tumors that showed no enhancement: low-grade gliomas (astro, oligo), ependymoma

- in presence of leaky tumor vessels there is some risk of precipitating seizure by iodinated contrast material used for CT scanning.
- H. pretreatment with 10 mg IV DIAZEPAM or 4 mg LORAZEPAM 10 min before contrast administration.

MRI WITH CONTRAST

- most sensitive test of choice for detection of brain tumor (MRI reveals greater extent of tumor than does CT!)
- MRI may detect additional tumors not suspected with CT!
  1) posterior focus tumors – no bony artefacts as in CT.
  2) low-grade gliomas – MRI shows extensive brain infiltration when CT fails to produce any image abnormality.
- most protocols include T1, proton density, and T2 images.
Many brain tumors will not be seen unless contrast medium is used (small lesions that lack mass effect and edema may only be detectable on contrast-enhanced MRI)

- delineates tumor in all three planes without requiring patient to change position.
- important application - use of sagittal MRI image in planning radiation treatment.
- MRI has supplanted CT as preferred test of choice in follow-up of patients undergoing active treatment.

**Features of tumors**

1) **signal alteration** - depends on MRI type, see below
   - irregular tumor borders suggest invasiveness (histologic malignancy).
   - **Feature that most affects MRI appearance is increased water content**

2) **mass effect** (volume of necrotic tissue + surrounding vasogenic edema)*
   - *malignant tumors are associated with considerable edema
   - MRI is more accurate than CT in defining extent of infiltrating tumor
   - features of extra-axial mass (differentiation from intra-axial mass)
     - ‘bucking’ and medial displacement of gray-white matter interface;
     - CSF cleft separating base of mass from adjacent brain.

3) **contrast enhancement** (reflects BBB breakdown in neovascular structures)
   - N.B.: volume of enhancement represent major tumor mass, but tumors cells typically extend beyond this boundary (important in planning therapy for MALIGNANT GLIOMAS).
   - contrast enhancement is sign of malignancy! (exceptions exist). see above >>
   - **degree of enhancement homogeneity** - more benign lesions tend to be more homogeneous.
   - border between tumor and edema may not be clear (important when planning biopsy);
   - neoplastic infiltration frequently extends some distance into zone of edema.
   - **intratumoral use** can significantly diminish contrast enhancement!!!
   - postoperative enhancement and radi necrosis may be difficult to distinguish from residual or recurrent tumor; consider TRAM protocol – see p. 81/1 >>

4) **neurologic core**
   - **how to distinguish from cystic tumor – DWI** (diffusion restriction in necrosis), GRE (old hemorrhagic cavity).
   - 5) peritumor edema – more pronounced in metastases, less in primary CNS tumors.

**T1 - well-demarcated area of low density.**

- **T1 with gadolinium – most precise way to image brain tumor**
  - patients can be followed up during and after treatment with T1 alone.

**T2 - bright whiteness** in more extensive region (signal of surrounding brain edema);

- **FLAIR - most precise way to spot brain tumor**
  - better contrast between normal and abnormal tissue than in T1.
  - **T2 may miss some brain metastases!!!**

- **tumors that are hypointense on T2**

**METASTATIC MALIGNANCIES** (paramagnetic properties of melanin)

**Dermoid (due to fat)**

**POURRI CYST**

**INTRATUMORAL HEMORRHAGE**

- also delineates demarculating effects of radiation (FLAIR, variant of T2, is even better for this).

**MENINGIOMAS** are usually **isointense** on all image sequences!!!

**Tumor type**  
**T1 with gadolinium**  
**Contrast CT**

**CHORIOCYSTOMA** ring configuration

**ADENOLIPOMA** solidly bright or patchy or do not enhance.

**LOW-GRADE ASTROCYTOMAS** do not enhance (except pilocytic astrocytoma) (invisible or vague low density)

**OLIGODENDROGLIOMAS** do not enhance (unless anaplastic) (invisible; unless calcified)

**PITUITARY ADENOMAS** always enhance less than normal pituitary gland.

**METASTASES** variable: some enhance brightly and solidly, others are in ring configuration (central necrosis & cavitation). CT is inferior in every way.

**ACOUSTIC NEUROMAS, MENINGIOMAS** intensely contrasted (= homogeneously) contrasted

**PINEAL Cysts** smoothly round homogeneous enhancement; paraventricular location is common; multiple in 25% cases (easily mistaken for metastases)

**MALIGNANT TUMORS** are detectable on contrast MRI: 

- hyperdense even without contrast (due to hypercellularity)

N.B. for tumors with propensit for leptomeningeal spread (MENINGEAL OXARTHROSIS, EPENDYMOMAS, CHORDOMA PLEXUS CARDIOMA, MALIGNANT PINDEL REGION TUMORS), spinal MRI must be done!

**Cyte + mural nodule**

1) pilocytic astrocytoma

2) pleomorphic xanthoastrocytoma (PKA)

3) hemangiblastoma

4) ganglioglioma, esp. desmoplastic infantile ganglioglioma / astrocytoma (DIG/DGIA)

5) metastasis

6) neurocytarcrosis

**Perfusion-weighted MRI (Pw-MRI)**

markedly increased tCBV - excess vascualrization (growth of high-grade tumors); increased tCBV - low-grade tumors; decreased tCBV - vasogenic edema - radiation necrosis.

**Tumors show diffusion restriction** (due to hypercellularity and proteinaceous stroma)

**Glioblastoma multiforme:**

A. T2-MRI shows only necrotic part of tumor (large arrows) and peritumoral edema (small arrows).

B. Diffusion-weighted MRI - solid parts of tumor (arrowheads) are well demonstrated.
**Diffusion Tensor Imaging (DTI)**
- shows tracts in peritumoral area - guides safer tumor resection.

**Generalized Q-Sampling Imaging**
- can visualize tracts in peritumoral edema even better than DTI.

**fMRI**
- presurgical evaluation of eloquent cortex. see also p. D66 >>
Alternative – intraoperative electrical cortical mapping.

**MRS**
- noninvasive in vivo method of analyzing tissue chemical spectrogram. see p. D53 >>

- commonest abnormalities in glioma (vs. necrosis)
  
  - increased: choline (membrane metabolism) / N-acetyl aspartate (living neurologic tissue)  
  - decreased - NAA/creatine.

- commonest abnormalities in radiation necrosis
  
  - increased - lipids/lactate (large peak)  
  - decreased - choline, N-acetyl aspartate, creatine.

- As comparison – infarction (stroke) region:

  - lactate↑, N-acetylaspartate (NAA)↓, creatine↓, choline↑  

  *choline is only difference from tumor

- commonest abnormalities in gliomas (vs. necrosis)

  - increased: choline (membrane metabolism) / N-acetyl aspartate (living neurologic tissue)  
  - decreased - NAA/creatine.

- Characteristic spectroscopic appearance of glioma - elevated choline (Cho) peak (3.22 p.p.m.), low creatine (PCr/Cr) peak (3.03 p.p.m.), nearly undetectable N-acetylaspartate (NAA) peak (2.01 p.p.m.):

  - Glioblastoma multiforme - elevated choline/creatine (Cho/Cr), persistent N-acetylaspartate (NAA) and lipids/lactate peaks:

![Glioblastoma multiforme](image)
BRAIN TUMORS (GENERAL)

PET

- tumor localization & specification:
  - characteristic of rapidly growing tumor is increased anaerobic glycolysis (FDG PET - high glucose utilization but low oxygen extraction).
  - tumor metabolic activity correlates with biologic aggressiveness - HIGH-GRADE Gliomas show more glycolytic activity than LOW-GRADE Gliomas.
  - preoperative PET localization of eloquent cortex - activation studies with H$_2^{15}$O.
  - tumors that respond to therapy become hypometabolic (before they shrink in size on MRI).
  - recurrent symptoms after radiation therapy:
    - recurrent / residual tumor (glycolytic activity↑)
    - radiation necrosis (glycolytic activity↓)
  - often appear identical on MRI / CT (contrast enhancement, mass effect, edema).

PET has great value in distinguishing tumor recurrence from radiation necrosis.

- false-positives: inflammatory cells in areas of radiation necrosis may show increased metabolic activity.
- false-negatives: tumor cells also may be present in areas of low glucose activity.

H$_2^{15}$O PET activation study (before neurosurgical resection) during language task - language activation is seen bilaterally and is distant from right frontal glioma.

Recurrent malignant glioma (after surgical resection, radiation therapy, and chemotherapy):
A) gadolinium-enhanced MRI - area of contrast enhancement.
B) PET with 18 F-deoxyglucose - region (corresponding to MRI enhancement) has increased metabolism compared with white matter (arrows).

Radiation necrosis (after surgical resection, radiation therapy, and chemotherapy):
A) gadolinium-enhanced MRI - area of contrast enhancement.
B) PET with 18 F-deoxyglucose - region (corresponding to MRI enhancement) has reduced metabolism compared with white matter (arrows).
**SPECT**

**Principal value - distinguishing tumor recurrence from radiation necrosis:**
- **[18]F-chloride SPECT:** can distinguish between HIGH-GRADE GLIOMAS (show increased uptake compared with normal brain parenchyma) and **LOW-GRADE GLIOMAS** (no increased uptake); can also distinguish CNS lymphoma (increased activity) from toxoplasmosis (decreased activity) in immuno-compromised patients.
- **[11]C-methyl tyrosine SPECT** shows uptake at sites of increased protein synthesis - used to distinguish **LOW-GRADE GLIOMAS** from benign lesions.

**Angiography:**
- **Chordoma**
- **Chemodectoma**
- **Pituitary adenoma**
- **Neuromas**
- **Meningioma**
- **EXTRA**
  - **Colloid cyst**
  - **Meningioma**
  - **Choroid plexus**
- **INTRA**
  - **Hemangioblastoma**
  - **Lymphoma**
  - **Metastases**
  - **Glioma (low grade)**
  - **Gliomas**
  - **Loefgren**

**MRI features and uniform histology**
- Biopsy is available from extra untreated cases.

**Increased vascularity:**
1. Increased vascularity
2. 
   - 
3. 

**Vascular displacement**
- May indicate tumor position relative to neuroaxis: superficial brain mass will compress vessels against cranial vault or falx cerebri, whereas one outside brain will separate them from those structures; mass within temporal lobe elevates MCA (MCA draped over expanded lobe).
- May indicate herniation. See p. 554.

**feeding vessels are close to tumor origin:** cerebral tumors are fed by cerebral vessels, choroid plexus tumors - by choroidal vessels, extracerebral tumors - by meningeval vessels.

**Exceptions:**
- **MENINGIOMAS** - not infrequently acquire pial supply.
- **GLIOMAS** and, particularly, **METASTASES** - dural supply is well documented.

<table>
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<th>Increased vascularity</th>
<th>Tumor vessels</th>
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<th>Venous filling</th>
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<td>++ to ++</td>
<td>to ++ early</td>
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</table>

**BIOPSY**
- definitive tissue diagnosis necessary for adequate treatment planning. See p. D34.
- **Primary brain tumors** are verified histologically (either resection surgery or biopsy for unresectable cases), but 80% metastatic tumors are diagnosed & treated empirically (if biopsy is available from extra-CNS locations).
- **Biopsy is not indicated in CHORDOMA GLIOMAS and DIFFUSE BRAIN STEM GLIOMAS** - characteristic MR imaging features and uniform histology - biopsy rarely influences treatment (prognosis is dismal in diffuse brain stem tumors regardless of biopsy results + biopsy is hazardous).
- **Unless brain stem glioma has exophytic component (which may be biopsied)**

Open biopsies (without tumor removal) are not justifiable! - if skull and dura are to be opened, surgeon should do gross total resection; however, if tumor is unresectable (due to eloquent infiltration) but close to cortex, open biopsy gives more material!!! (Dr. Cohen-Gadol)
All brain regions may be approached by MR-guided stereotactic biopsy:
- Stereotactic biopsy usually provides enough tissue to make diagnosis of glioma but may not provide enough to grade tumor (most informative specimen is one taken from area of contrast enhancement).
- Gliomas are heterogeneous - areas of low-grade histology are commonly noted in many high-grade tumors!
- Stereotactic biopsy is reserved for poor-surgical risk patients (but if tumor has prominent blood vessels or hemorrhage within tumor, open biopsy is preferable).
- Open excision may result in unacceptable functional impairment without positive influence on survival.

**DIFFERENTIAL DIAGNOSIS**

1. Hematomas (may be mistaken for acute bleeding into tumor)
2. Abscesses*
3. Granulomas*
4. Parasitic infections (such as cysticercosis)
5. Vascular malformations (esp. without AV shunts)
6. Solitary large MS plaque, concentric sclerosis of Balo (but T2-MRI usually reveals additional asymptomatic lesions)
7. Progressive strokes (rare)

*usually cannot be distinguished from tumors by CT or MRI alone - reliable management may demand biopsy.

**HYDROCEPHALUS**

A. Obstructive hydrocephalus - obstruction at ventricular atrium → foramen of Monro → aqueduct → 4th ventricle.
   - tumor can act as valve (e.g. tumor in region of foramen of Monro) → sudden potentially life-threatening hydrocephalus.
B. Communicating hydrocephalus
   a) tumor seeding to meninges
   b) reaction to previous therapy

- if depressed consciousness persists despite steroid administration, CSF diversion procedure should be strongly considered.

**INTRATUMOR HEMORRHAGE**

- tumors that most often cause hemorrhage (stroke-like onset of focal neurologic deficit):
  1) oligodendrogliomas, high-grade astrocytomas
  2) some metastatic tumors (melanoma??, renal cell carcinoma, choriocarcinoma, testicular carcinoma)
  3) WNT among medulloblastomas

- may be provoked by iatrogenic thrombocytopenia (associated with chemotherapy).
- clinically: insignificant + dramatic.
- treatment: - osmotic agents and glucocorticoids a surgical decompression.

**COMPLICATIONS**

**BIBLIOGRAPHY**

for ch. “Neuro-Oncology” → follow this link >>

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any tumor causing mass effect or neurologic symptoms in relatively noneloquent area of brain should be removed (as biopsy is part of surgical resection)