Brain Tumors (GENERAL) Last updated: September 5, 2017

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41. CELL OF ORIGIN

- 1-1.2% of all cancers.
- 1% of all cancer deaths.
- 20% of total annual cost of cancer treatment is for CNS cancers (primary or metastatic).
- median age-adjusted incidence (for primary brain tumors) = 2.15 cases per 100,000 per year.
- incidence of brain tumors continues to increase:
  - 6th most common cancer in adults.
- pediatric incidence (for primary brain tumors) = 1.3 pediatric cases per 100,000 per year.
- after leukemia, second most common cancer in children (20% pediatric tumors).
- two peaks of incidence:
  - small peak in childhood (predominance of ependymal CNS neoplasms and relative absence of gliomas) → drops slightly in adolescence → rises steadily → much higher peak in 60-80 years (predominance of supratentorial gliomas)
- men ≥ women (except meningiomas ← women : men = 2:1).
- incidence of brain tumors continues to increase:
  - 6th most common cancer in adults.

Epidemiology

Neoplastic transformation can occur in:

1. neuroglia → gliomas: most commonly encountered (50-60%) and most feared brain tumors!
   - astrocyte → astrocytoma (incl. glioblastoma multiforme)
   - oligodendroglioma → oligodendroglioma
   - ependymoma → ependymoma, ependymoblastoma
2. neurons (almost exclusively postmitotic - not at risk for becoming tumor) or neuroblast → ganglioglioma, nerveblastoma, retinoblastoma
3. primitive neuroectoderm → medulloblastoma
4. choroid epithelial cell → choroid plexus papilloma / carcinoma
5. arachnoidal fibroblast → 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 (neurilemoma)
11. primary lymphocytes → CNS lymphoma
12. primitive germ cells → germoma, pinealoma, teratoma, cholesteatoma
13. melanocyte → melanotic carcinoma
### 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>Name</th>
<th>Genetic Features</th>
<th>WHO 2016</th>
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</thead>
<tbody>
<tr>
<td>Diffuse astrocytoma, IDH-mutant</td>
<td>IDH-mutant</td>
<td>Diffuse astrocytoma, IDH-mutant (WHO 2016)</td>
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<tr>
<td>Anaplastic astrocytoma, IDH-mutant</td>
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<td>1p/19q-codeleted</td>
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<tr>
<td>Oligoastrocytoma, NOS</td>
<td>NOS</td>
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<tr>
<td>Anaplastic astrocytoma</td>
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<td>Other ependymal tumours</td>
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<td>Pilocytic astrocytoma</td>
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<td>Subependymal giant cell astrocytoma</td>
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<td>Subependymoma</td>
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<td>Papillary ependymoma</td>
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<td>Anaplastic papillary ependymoma</td>
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<tr>
<td>Other gliomas</td>
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<td>Oligoastrocytoma, IDH-mutant and 1p/19q-codeleted</td>
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<td>Gangliogliomas</td>
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</table>
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 glioneuronal tumor (entity)
   6) Anaplastic PXA (entity)
   7) Epithelioid glioblastoma (variant)
   8) Glioblastoma with primitive neural component (pattern)
   9) Multinodular and vacuolated pattern of ganglion cell tumor (pattern)
8. Deletion of former entities, variants and terms:
   1) Gliomatosis cerebri
   2) Protoplaxic and fibrillary astrocytoma variants
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 adopting 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 hematopoietic/lymphoid tumors of the CNS (lymphomas and histiocytic tumors)
Gliomas are not divided sharply into benign and malignant forms; rather, they represent gradations on spectrum from slowly growing to rapidly growing neoplasms. 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).

b) immunohistochecmical staining with antibodies to proliferating cell nuclear antigen (PCNA).
c) immunohistochecmical staining with Ki-67 antibody (recognizes histone protein expressed in proliferating but not quiescent cells).

Older WHO

NEUROEPITHELIAL TUMORS

1. ASTROCYTIC TUMORS
   a) (juvenile) pilocytic astrocytoma (non-invasive, WHO grade I)
   b) desmoplastic
   c) opte
   d) brain non
   e) cerebellar
   2. subependymal giant cell astrocytoma (non-invasive, WHO grade I)
   3. pleomorphic xanthoastrocytoma (WHO grade I)
   4. astrocytoma (WHO grade II)
      a) pulmonary
      b) desmoplastic
      c) opte
      d) brain non
      e) cerebellar
   5. anaplastic (malignant) astrocytoma (WHO grade III)
      a) pulmonary
      b) desmoplastic
      c) opte
      d) brain non
      e) cerebellar
   6. glioblastoma multiforme (WHO grade IV) – most aggressive and most common of all CNS tumors!!!
      variants: giant cell glioblastoma, gliosarcoma

2. OLIGODENDROGIAL TUMORS
   a) oligodendroglioma (WHO grade II) = 80%
   b) anaplastic (malignant) oligodendroglioma (WHO grade III) = 20%

3. EPENDYMAL CELL TUMORS
   a) subependymoma (WHO grade I)
   b) ependymoma (WHO grade II)
      variants: cellular, papillary, epithelial, clear cell, mixed
   c) anaplastic ependymoma (WHO grade III)
   d) myxopapillary ependymoma

4. MIXED GLIOMAS
   a) mixed oligoastrocytoma (WHO grade II)
   b) anaplastic (malignant) oligoastrocytoma (WHO grade III)
   c) others (e.g. ependymoastrocytoma)

5. Neuroepithelial tumors of uncertain origin
   a) polar spongioblastoma (WHO grade IV)
   b) astroblastoma (WHO grade IV)
   c) gliomatosus cerebel (WHO grade IV)

6. Tumors of choroid plexus
   a) choroid plexus papilloma (66-90%)
   b) choroid plexus carcinoma (anaplastic choroid plexus papilloma) (10-33%)

7. NEURONAL AND MIXED NEURONAL-GLIAL TUMORS
   a) gangliocytoma (s. central ganglionneuroma) – neuronal tumor; benign counterpart of neuroblastoma in CNS
   b) dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)
   c) ganglioglioma – glioma with glial component
   d) anaplastic (malignant) ganglioglioma
   e) desmoplastic infantile ganglioglioma
   f) central neurocytoma – tumor of well-differentiated neurons
   g) dysembryoplastic neuroepithelial tumor (DNET) – benign mixed glial-neuronal tumor
   h) olfactory neuroblastoma (esthesioneuroblastoma)
      variant: olfactory neuroblastoma

8. PINEAL PARENCHYMAL TUMORS
   a) pineocytoma (WHO grade I)
   b) pineoblastoma (WHO grade IV)
   c) pineal parenchymal tumor of intermediate differentiation (WHO grade II-II)
   d) papillary tumor of pineal region (WHO grade II-II)

9. Tumors with neuronlastic or glioblastic elements (s. embryonal tumors)
   a) medulloblastoma
      variants: medulloblastoma, desmoplastic, medulloblastoma
   b) primitive neuroectodermal tumor (PNET)
   c) neuroblastoma
      benign counterparts: ganglioneuroblastoma, ganglieneuroma (s. ganglioma)
1. Tumors of SELLAR REGION
   1) pituitary adenoma
   2) pituitary carcinoma
   3) craniopharyngioma

2. HEMATOPOIETIC TUMORS
   1) primary malignant lymphomas
   2) plasmacytoma
   3) granulocytic sarcoma

3. GERM CELL TUMORS
   1) germinoma
   2) embryonal cell carcinoma
   3) yolk sac tumor (endodermal sinus tumor)
   4) choriocarcinoma
   5) teratoma
   6) mixed germ cell tumor

4. Tumors of MENINGES
   1) meningioma
      variants: meningothelial, fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, secretory, clear cell, chordoid, lymphoplasmacytoid, metastatic subtypes
   2) atypical meningioma
   3) anaplastic (malignant) meningioma

5. NON-MENINGOTHelial TUMORS OF MENINGES
   1) benign mesenchymal
      a) osteocartilaginous tumors
      b) lipoma
      c) fibrous histaicystoma
   2) malignant mesenchymal
      a) chondrosarcoma
      b) hemangiospericystoma
      c) rhabdomyosarcoma
      d) meningeval sarcomatosis
   3) primary melanotic lesions
      a) diffuse melanosis
      b) melanocytoma
      c) malignant melanoma
         variant: meningeval melanomatosis

4. Hemopoietic neoplasms
   a) malignant lymphoma
   b) plasmacytoma
   c) granulocytic sarcoma
   d) tumors of uncertain histogenesis - hemangioblastoma (capillary hemangioblastoma)

6. Tumors of CRANIAL / SPINAL NERVES
   1) neurofibroma
   2) schwannoma (neurinoma, neurilemoma)
      subtypes: cellular, plexiform, melanotic
   3) malignant peripheral nerve sheath tumor
      variants: epithelial, desmoplastic, neural, melanotic, differentiation, melanotic

7. CYSTS and TUMOR-LIKE LESIONS
   1) Rathke cleft cyst
   2) epidermoid cyst
   3) dermoid cyst
   4) colloid cyst of 3rd ventricle
   5) enterogenous cyst
   6) neuroglial cyst
   7) granular cell tumor (choristoma, pituicytoma)
   8) hypothalamic neuronal hamartoma
   9) nasal glial heterotopia
   10) plasma cell granuloma

8. LOCAL EXTENSIONS from regional tumors (i.e. secondary intracranial tumors)
   1) paraganglioma (chemodectoma)
   2) chordoma
   3) chondroma
   4) chondrosarcoma
   5) carcinoma

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

10. UNCLASSIFIED TUMORS

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CONGENITAL NEOPLASMS

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

FREQUENCY
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).

| Extra-axial | % | Primary Metastatic ** |
|-------------|--|--|-------------------|
| Glioblastoma | 16 | Lung (37-49) |
| Acoustic neuroma (24) | 8 | Breast (16-19) |
| Anaplastic astrocytoma (15) | 15 | Melanoma (16) |
| Oligodendroglioma (5) | 4 | Other (3) |
| Lymphoma (2.7) | 2 | Kidney (8) |
| Other (7) | 5 | Other (11) |

*in childhood, craniopharyngioma and pineal region tumors are most common.
**in childhood, most common metastatic tumors are neuroblastoma (usually epidural) and leukemia (meningeal).

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.

**PATHOLOGY**

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. Cerebral astrocytomas
3. around Ependymomas
4. Alexander disease (Rosenthal fibers radiate from vessels)

Rosenthal fibers in neuronal

**BENIGN vs. MALIGNANT**

1/3 brain tumors can be called MALIGNANT (mainly extra-axial tumors - meningiomas, acoustic neuromas).

Concept of malignancy in CNS has different meaning 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.
  2. anatomic location - can have lethal consequences irrespective of histologic classification.
  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. glioma 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 FOLLICULAR SARCOMA may invade adjacent dura mater and bone and grow into cavernous or sphenoid sinuses.
- e.g. malignant GYNERIONTOMA MULTIFORME 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) – glomas and metasteses, meningiomas.

most common tumors below tentorium (intra-axial tumors predominate) – neureomas, metasteses 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.

<table>
<thead>
<tr>
<th>Age</th>
<th>Hemispheres</th>
<th>Diencephalon</th>
<th>Posterior Fossa</th>
<th>Meninges</th>
<th>Spinal Cord</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adulthood</strong></td>
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<tr>
<td></td>
<td>Astrocytoma, oligodendrocytoma, metastases, lymphomas</td>
<td>Astrocytoma, colloid cyst, primary alecroma</td>
<td>Metastases, hemangioblastoma</td>
<td>Metastoma, CNS schwannoma, menetares, lymphoma</td>
<td>Metastoma, menengioma, nerve sheath tumors, astrocytoma, ependymoma</td>
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<td><strong>Childhood</strong></td>
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<tr>
<td></td>
<td>Astrocytoma, ependymoma, choroid pleural tumor, primitive neuroectodermal tumor</td>
<td>Germ cell tumors, craniopharyngioma</td>
<td>Medulloblastoma!!!, ependymoma, cerebellar pleyic astrocytoma, brain stem astrocytoma, choroid pleural tumor</td>
<td>Laksoma, lymphoma</td>
<td>Nerve sheath tumors, astrocytoma</td>
</tr>
</tbody>
</table>

**Distribution of intracranial tumors in adults**

- **Frontal**: Medulloblastoma, ependymoma, acoustic neuroma, glioblastoma multiforme, meningioma, craniopharyngioma.
- **Temporal**: Medulloblastoma, ependymoma, acoustic neuroma, glioblastoma multiforme, meningioma, craniopharyngioma.
- **Parietal**: Medulloblastoma, ependymoma, acoustic neuroma, glioblastoma multiforme, meningioma, craniopharyngioma.
- **Occipital**: Medulloblastoma, ependymoma, acoustic neuroma, glioblastoma multiforme, meningioma, craniopharyngioma.
BRAIN TUMORS (GENERAL)

INTRAVENTRICULAR TUMORS

Tumor | Typical site
---|---
CIS | Foramen of Monro / 3rd ventricle
SEG | Foramen of Monro
MENINGIOMA | Trigone of lateral ventricle
CHORDOPLAXIS PAPILLOMA | 3rd ventricle
EPENDYMOMA | Lateral ventricle (more common in children), 4th ventricle
SUBEPENDYMOMA | Lateral ventricle, 4th ventricle
NEUROCYTOMA* | Lateral ventricles (involving septum pellucidum)
METASTASES | Lateral ventricles, ependyma and choroid plexus

*most common lateral ventricle tumor in young adults

Differentials:
Neurocysticercosis

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%)
PRIMARY NEUROECTODERMAL TUMORS, incl. MEDULLOBLASTOMA (10-20%)
EPENDYMOMA (11%)
CHOROID PLEXUS CARCINOMA (10-20%)
OLIGODENDROGLIOMA (1%)
PINEAL GERMINOMA (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).

Brain tumors cause death by local growth!

Tumor BURDEN

- tumor mass of 30-60 g (3.6 x 10^{10} cells) usually produces neurologic symptoms.
- brain cancer is lethal when 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.

CELLULAR HETEROGENEITY

- parental cell population is genetically unstable → tumors are heterogeneous in cellular content:
a) genotypic (incl. 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 histologic appearance).

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

TUMOR MARKERS

- see Intro (oncology)

ETOLOGY, 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.

- see Intro (oncology)
Tumor suppressor genes associated with nervous system tumors

- **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 lymphoma 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.

## Tumor suppressor genes associated with nervous system tumors:

### Tumor suppressor genes associated with nervous system tumors:

- **p53** (Tp53) – loss predisposes to astrocytoma and neurofibrosarcoma.
- progression from low-grade astrocytoma to glioblastoma strongly correlates with loss of p53 gene.
- Li-Fraumeni syndrome - familial cancer syndrome in young adults (< 45 yrs) - breast cancer, soft tissue sarcomas, brain tumor (esp. astrocytoma, osteosarcoma, leukemia, adrenocortical carcinoma.
- affected people inherit one mutant p53 allele.
- sporadic (nonfamilial) forms of cancers associated with Li-Fraumeni syndrome also show p53 inactivation.
- **NF1** (17q11.2), **NF2** (22q12) - loss predispose to neurofibromatosis.

### 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>
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<tbody>
<tr>
<td>neurofibromatosis type 1</td>
<td>von Recklinghausen’s disease</td>
<td>NF1 (17q11)</td>
<td>Neurofibroma, malignant peripheral nerve sheath tumor (MPNST), meningioma, optic nerve glioma, (low-grade) astrocytoma</td>
</tr>
<tr>
<td>neurofibromatosis type 2</td>
<td>NF2 (22q12)</td>
<td>Bilateral vestibular schwannoma, peripheral schwannoma, meningiomas, astrocytoma, neurinomas, spinal epinephyma, glial hamartias, cerebral calcification</td>
<td>Retinal hamartomas, skeletal lesions, cutaneous angiofibroma, renal cell carcinoma, phaeochromocytoma, visceral cysts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Nervous Tumor</th>
<th>Other tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Hippel-Lindau syndrome</td>
<td>VHL (3p25)</td>
<td>Hemangio/blastoma</td>
<td>Renal hemangio/blastoma, renal cell carcinoma, phaeochromocytoma, visceral cysts</td>
</tr>
</tbody>
</table>

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<tr>
<th>Syndrome</th>
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<tbody>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1 (9q34), TSC2 (16p13)</td>
<td>Subependymal giant cell astrocytoma (SEGAs), cortical tubers</td>
<td>Cardiac rhabdomyoma, adenomatous polyposis of small intestine, cysts of lung and kidney, renal angiomyolipoma, lymphangioleiomyomatosis, cutaneous angiofibroma, subependymal fibroma</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>p53 (17p13)</td>
<td>various malignant gliomas, PNET (medulloblastoma)</td>
<td>Breast carcinoma, bone and soft tissue sarcoma, adrenocortical carcinoma, leukemia</td>
</tr>
</tbody>
</table>
Multiple endocrine neoplasia type 1

not known

pulmonary adenomas, malignant schwannoma

Rathke cleft cyst

ependymoblastoma, pineoblastoma

Tumour syndrome

APC (5q21), SMAD4 (18q21), TP53 (17p13)

GBM, medulloblastoma

Colorectal polyposis

Werner’s syndrome

WRN (6p12)

Meninergia

Covidi disease (multiple hamartoma syndrome)

PTEN (10q23)

Displastic gangliocytoma of cerebellum (Lhermitte-Duclos), megalencephaly

Hamartomas of skin, GI tract, gonadal fibromatosis, multiple tricholemmoma, thyroid neoplasms, breast carcinoma

Gorlin syndrome (nevoid basal cell carcinoma syndrome)

PTCH (9q31)

Medulloblastoma (in > 5% mutation carriers)

autosomal dominant - combination of sebaceous gland tumors at least one visceral cancer.

malignancies characterized by microsatellite instability.

Maffucci syndrome (eccoulovascular dysplasia)

MELH, MLH1 - DNA mismatch repair genes (subtypes of Lynch Type II hereditary nonpolyposis colon cancer (HNPCC))

autosomal dominant - combination of sebaceous gland tumors at least one visceral cancer.

malignancies characterized by microsatellite instability.

Godman syndrome (scollovalveal dysplasia)

intracranial dermoids, lipomas of corpus callosum

Shwachman syndrome (pancreatic exocrine insufficiency, bone marrow and hematopoietic dysplasia, skeletal and craniofacial dysmorphism, congenital pneumonia, interstitial lung disease, megalencephaly, intellectual disability, skeletal dysplasia, gynecomastia, short stature, adrenal insufficiency, deafness, and lymphatic anomalies)

- Autosomal recessive
- Autosomal dominant
- X-linked

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")

- formerly, it was thought that edema in adjacent white matter is result of diffusion of fluid from tumor.

- e.g. 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 not unusual for 20 g tumor to produce 100 ml mass because of associated edema.

Pathophysiology of clinical features

Intra-axial tumors produce symptoms by three mechanisms:

A. Tumors 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. Tumors 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. Tumors infiltrate, grow as mass, and destroy surrounding neurite (malignant glioma) → generalized and focal symptoms, which 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):

a. intraventricular (at Monro foramen, aqueduct, 4th ventricle)

b. leptomeningeal or carcinomatous involvement of meninges

4) 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.

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).
N.B. symptoms in young children and infants are nonspecific and are frequently mistaken for non-CNS problems - diagnosis of pediatric brain tumor can be extremely difficult to make without very high index of suspicion!

2. Primary histology - determines rate of symptom evolution. e.g. benign tumors may achieve considerable size before producing symptoms (grow slowly, cerebral edema occurs infrequently).

3. Tumor location

- e.g. extra-axial tumors - usually well circumscribed with benign histology - clinical presentation is directly related to CNS structures immediately adjacent to lesion. e.g. posterior fossa tumors or cerebellum may present with vomiting and following symptoms:
  - Deterioration in mental status
  - Headache
  - Intense paroxysmal headaches
  - Nausea - relatively late sequela
  - Seizures - perhaps most significant of "classic" brain tumor headache
  - Projectile vomiting - N.B. "projectile" is misnomer
  - N.B. symptoms in young children an
  - Intense photophobia

Symptoms do not differ much by tumor histology but rather relate to area of brain affected.

**Asymptomatic cases**

1. silent areas (tumors may grow large; parietal or frontal association cortices, nondominant 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):**

- **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 (useful in assessing and following patients with CNS neoplasms):

- 100 – Normal (no evidence of disease)
- 90 – Minus 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
- 20 – Active supportive treatment needed (very sick)
- 10 – Moribund

**WHO performance scale**

- Grade: Definition
- 0 Fully active, able to carry on all pre-disease performance with no restriction
- 1 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.
- 2 Ambulatory and capable of all self care, but unable to carry on any work activity. Up and about more than 50% of waking hours.
- 3 Capable of only limited self care, confined to bed or chair more than 50% of waking hours
- 4 Completely disabled. Cannot carry out any self care. Totally confined to bed or chair
- 5 Dead

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 sequelae occurs in:
  - 50-60% primary brain tumors,
  - 35-50% metastatic tumors.

- rare as initial symptom in brainstem tumors, cerebellopontine angle tumors, pituitary tumors, craniopharyngiomas.
- about features of "classic" brain tumor headache – see p.50 >>
  - typically semilocalized in vicinity of tumor (e.g. worse on side of tumor); posterior fossa tumors may present with pain referred to occipital region.
- may present with pain referred to occipital region. In series of 111 patients, headache had characteristics similar to migraine in 9% and tension type headache usually.
- head down, loss vision, consciousness falls.

**Intense paroxysmal headaches** may develop abruptly (within seconds); last only 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 falls.
- possible mechanism - acute hydrocephalus (ball-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, delirium)

- 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.

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

No pattern is diagnostic of brain tumor!

**BCP**!
4. Cushing reflex - signals life-threatening CP;[\textsuperscript{9}]. see p. S50 >\textsuperscript{9}

5. Brain mass shifts - may manifest as focal neurological signs - CN6 palsy, CN3 palsy, ipsilateral hemiparesis (compression of opposite cerebral peduncle against Kernohan’s notch), ipsilateral visual field defects (compression of opposite PCA), mastic rigidity & torticollis\textsuperscript{*} (nervation 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 
  - neuroaxis and white matter tracts by expanding tumor and accompanying edema.
- vascular compression may produce focal brain ischemia.

1. Seizures - occur in 20-71% patients (as presenting symptom in 18-50% cases);

- focal or generalized
- most common with QUIESCENT tumor affecting cortex (esp. meningiomas, oligodendroglialomas, 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\textsuperscript{*}, resistance to medical control, focal symptoms.
  - *brain tumor patients have higher incidence of postictal neurologic deficit!

2. Negative signs - hemiparesis, sensory loss, aphasia, cranial nerve palsies, visual deficits, hearing impairment, amnesia, personality changes, etc.

- multiple metastases cause diffuse brain infiltration (by glioma or lymphoma) may present as dementia or decline in level of alertness.
- hand preference in child < 3 yrs may signify hemiparesis.

3. Hyperactive function

- pinnutary / pinal tumors \(\rightarrow\) hormone overproduction.
- choroid plexus papilloma \(\rightarrow\) CSF overproduction.

**REGIONAL FEATURES**

**SUPRATENTORIAL TUMORS**

- progressive focal neurologic signs and symptoms predominate:

**Frontal lobe**

1. Seizures - may precede other symptoms by months or years.
2. Intellectual impairment (esp. with bilateral tumors, e.g. butterfly glioma)
3. Impairment of initiative and spontaneous activity; abulia \(\rightarrow\) akinetetic mutism.

4. Personality changes: see also p. Psy5 \(\rightarrow\)

- a) dorsolateral prefrontal lesions \(\rightarrow\) aphasic & indifferent (pseudopressedness)
- b) orbital prefrontal lesions \(\rightarrow\) loss of inhibition & euphoric (pseudopsychopathic).

7. Anosmia (e.g. meningioma of olfactory groove).

**Temporal lobe**

1. Personality change (bizarre thinking, trance-like states, mood symptoms, immature emotional behavior, bilateral amygdaloid lesions \(\rightarrow\) Klüver-Bucy syndrome).
2. Sensory aphasia, anoma.
4. Contralateral hemianopsia (or superior quadrantopsia).
5. Impairment of recent memory (bilaterial hippocampal lesions \(\rightarrow\) Korsakoff amnesia).

**Parietal lobe**

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

**Occipital lobe**

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

**Basal Ganglia**

1. Hydrocephalus.
2. Contralateral sensory abnormality, neurogenic pain, intermittent paresthesias.
3. Involvement of 
   - basal ganglia \(\rightarrow\) contralateral intention tremor, hemiballistic movement.
4. Involvement of 
   - hypothalamus \(\rightarrow\) eating disorders, precocious puberty.

**Posterior Fossa**

- tumors occupying more of limited space + vital brain stem nuclei
  1) early CSF flow obstruction \(\rightarrow\) hydrocephalus (rarely 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**

**Rhinorrhea**

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

*vs. CNS metastases, depending on primary tumor, may be associated with systemic features of malignancy.

- polyserositis associated with cerebellar tumor - presumptive evidence of MENINGIOMATOSIS.
# Tumor Markers

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

<table>
<thead>
<tr>
<th>Marker</th>
<th>Tumor types containing positive cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glial fibrillary acidic protein</td>
<td>Acroactoma, epidermoid, mixed glioma, gliosarcoma, ganglioglioma, glioblastoma multiforme, glioblastoma</td>
</tr>
<tr>
<td>Occasionally - oligodendrocytoma, capillary hemangioblastoma, choroid plexus papilloma, primitive neuroectodermal tumor</td>
<td></td>
</tr>
<tr>
<td>Neurofilament proteins</td>
<td>Ganglioglioma, gangliocytoma, primitive neuroectodermal tumor, neurocytoma, subependymal giant cell tumor</td>
</tr>
<tr>
<td>Vimentin</td>
<td>Mesenchymal tumors, meningiomas, sarcoma, melanoma, lymphoma, epidermoid, astrocytoma, glioblastoma, chordoma, schwannoma, hemangioblastoma, carcinoma, primitive neuroectodermal tumors, rhabdoid tumor</td>
</tr>
</tbody>
</table>

| S 100, neuron-specific enolase | Questionable utility - positive in normal and neoplastic cells of neural and non-neural origin |

Desmin
- Tumors containing muscle (rhabdomyosarcoma, teratoma, etc.), primitive neuroectodermal tumor

Cytookeratin
- Chordoma, chordoid plexus tumors, meningioma, certain anaplastic gliomas, nongerminomatous germ cell tumors, primitive neuroectodermal tumor

Epithelial membrane antigen
- Meningioma, epidermoid, epithelial areas of teratomas, rhabdoid tumor

Synaptophysin
- Primitive neuroectodermal tumor, ganglioglioma, gangliocytoma, central neurocytoma, neuroendocrine tumors

Retinal S-antigen
- Pineal parenchymal tumors, primitive neuroectodermal tumors, retinoblastoma

α-fetoprotein
- Embryonal carcinoma, endodermal sinus (yolk sac) tumor

Human chorionic gonadotropin
- Germ cell, choriocarcinoma

Placental alkaline phosphatase
- Germin cell tumors

# 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)

# OPTICHEALCOPAN

1. Papilledema - most reliable sign of ICP↑ (but present in only ≈ 20% patients)  
   - more common with tumors that occlude CSF ways – infratentorial, pineal, thalamic, 3rd ventricle tumors.

2. Other signs of ICP↑
   - see p. S50 >>

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

# SKULL X-RAY

- only rare indications:
  1. screening skull for metatropic disease
  2. assessing integrity of various sinuses

- may show signs of raised ICP.
  - see p. S50 >>

- tumor calcification.

- meningioma: hyperostotic bone reaction, enlargement of middle meningeal artery grooves.

- DERMOMATYS, ADRENOMATYS: bone thinning --> enlargement of middle cranial fossa or internal auditory meatus.

# PNEUMENCEPHALOGRAPHY

- historical method for diagnosing brain tumors.

# CSF

- LP should not be performed if intracranial mass is suspected!!!

- does not provide significant diagnostic information: raised opening pressure, protein↑, mild lymphocytic pleocytosis.

- ASTROCYTOMA that extend to ventricular surface, or EPIDERMOID CYST rupture, can produce intense CSF inflammation simulating infections meningitis.

- positive CSF cytology postoperatively is common, but seeding and new growth may not occur.

- indications - diagnosing:
  1. neoplastic meningitis (malignant cells in CSF) – LP indicated only if:
     a) symptoms suggest meningeal involvement.
     b) parenchymal mass has propensity to seed (e.g. MEDULLOBLASTOMA, EPENDYMOMA, CHORDOID PLEXUS CARCINOMA). 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.

- 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.

# EEG

- no role in diagnosis of brain tumors, does not assist in choice of anticonvulsant drugs.

- 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.
**OTOLARYNGOLOGY**

- Audiolometry, auditory evoked potential testing, electronystagmography - for tumors of cerebellopontine angle or posterior skull base.

**NEUROIMAGING**

- CT or MRI

- Most acute test for choice of detection of brain tumor (MRI reveals greater extent of tumor than does CT!).

- MRI may detect additional tumors not suspected with CT, eg:
  1. Posterior fossa tumors — no bony artefacts as in CT
  2. Low-grade gliomas — MRI shows extensive brain infiltration when CT fails to produce any image abnormality

- MRI is not superior to CT in specificity.

- MRI is more accurate (than CT) in differentiating lesions.

- MRI better delineates tumor in all three planes.

- Most protocols include T1, proton density, and T2 images.

- Contrast enhancement is significant in malignant tumors.

- Most sensitive test

- Most common screening examination

- Indispensable component of modern diagnosis

- MRI: pretreatment with 10 mg IV diazepam or 4 mg lorazepam 10 min before contrast administration.

- MRI reveals greater extent of tumor than CT.

- MRI with contrast:
  - Most common screening examination (but MRI is test of choice!)

CT without contrast enhancement is of little value in diagnosis of brain tumors or other mass lesions!

- Better definition (than MRI) of calcification — suggests more indolent growth; tumors that tend to calcify, oligodendrogliomas (90%), meningiomas, craniopharyngioma, teratoma, chordoma, choroid plexus tumors, ependymoma, central neurocytoma.

- CT preferable (over MRI) for evaluating bones, intramural hemorrhage.

- CT-guided localization (in stereotactic biopsies) is more precise than MRI because of "MRI distortion."

- On enhanced CT — most commonly as ring-like hyperdense region around central radiolucent area. Enhancement is stronger with more malignant tumors.

- 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! (exceptions exist)

**Features of tumors**

- In presence of leaky tumor vessels there is some risk of precipitating seizure by iodinated contrast material used for CT scanning.

- Adjacent swelling, vasogenic edema (reflects BBB breakdown and increased water content)

- Border between tumor and edema may be unclear (important when planning biopsy)

- Neoplastic infiltration frequently extends some distance into zone of edema.

- Corticosteroid use can significantly diminish contrast enhancement!!

**Features of tumors**

- Signal alteration — depends on MRI type. See below
  - Irregular tumor borders suggest invasiveness (histological malignancy)
  - Feature that most affects MRI appearance is increased water content

- Mass effect (volume of neoplastic 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):
    - Buciking and medial displacement of gray-white matter interface;
    - CSF cleft separating base of mass from adjacent brain.

- Contrast enhancement (reflects BBB breakdown in neovascular structures)

**CT WITH CONTRAST**

- Most common screening examination

- Indispensable component of modern diagnosis

- MRI is not superior to CT in specificity.

- Tumors that enhanced strongly: meningiomas, neurectomas, pilocytic astrocytoma, malignant tumors (high-grade gliomas, metastases, CNS lymphoma)

**MRI WITH CONTRAST**

- Most acute test for choice of detection of brain tumor (MRI reveals greater extent of tumor than does CT!).

- MRI may detect additional tumors not suspected with CT, eg:
  1. Posterior fossa tumors — no bony artefacts as in CT
  2. Low-grade gliomas — MRI shows extensive brain infiltration when CT fails to produce any image abnormality

- MRI is more accurate (than CT) in differentiating lesions.

- MRI better delineates tumor in all three planes.

- 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 therapy.

- Features of tumors
  1. Signal alteration — depends on MRI type. See below
  2. Mass effect (volume of neoplastic 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):
      - Buciking 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)

- Volume of enhancement represent major tumor mass, but tumor cells typically extend beyond boundary (important in planning therapy for malignant gliomas)

- Contrast enhancement is sign of malignancy! (exceptions exist). See above.

- Degree of enhancement homogeneity varies - 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.

- Corticosteroid use can significantly diminish contrast enhancement!!
• postoperative enhancement and radionecrosis may be difficult to distinguish from residual or recurrent tumor.

T1 - well-demarcated area of low density

• patients can be followed up during and after treatment with T1 alone.

T2 - bright whiteness in more extensive region (signal of surrounding brain edema);
• better contrast between normal and abnormal tissue than in T1.
• T2 may miss some brain metastases!!!
• tumors that are hypointense on T2

Glioblastoma multiforme
Tumors show Cyst + mural nodule

N.B. for tumors with MENINGIOMAS
T2 T1 COLLOID CYSTS INTRATUMORAL HEMORRHAGE
• T2 also delineates demyelinating effects of radiation (FLAIR, variant of T2, is even better for this).

MENINGOMAS are usually isointense on all image sequences!!!

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>T1 with gadolinium</th>
<th>Contrast CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLIOBLASTOMA</td>
<td>ring configuration</td>
<td></td>
</tr>
<tr>
<td>ANAPLASTIC ASTROCYTOMA</td>
<td>solidly bright or patchy or do not enhance.</td>
<td></td>
</tr>
<tr>
<td>LOW-GRADE ASTROCYTOMA</td>
<td>do not enhance (except pilocytic astrocytoma).</td>
<td></td>
</tr>
<tr>
<td>OLIGODENDROCYTOMA</td>
<td>do not enhance (unless anaplastic).</td>
<td></td>
</tr>
<tr>
<td>PITUITARY ADENOMAS</td>
<td>always enhance less than normal pituitary gland.</td>
<td></td>
</tr>
</tbody>
</table>

• tumors that are hypointense on T2

METASTASES
variable: some enhance brightlly and solidly, others are in ring configuration (central necrosis & cavitation). Many are invisible.

ACOUSTIC NEUROMA, MENINGOMA
intensely contrasted (≠ homogeneous) contrasted.

PRIMARY CNS LYMPHOMA
smoothly rounded homogeneous enhancement; prventricular location is common; multiple in 25% cases (easily mistaken for metastases).

hypodense even without contrast (due to hypercellularity).

N.B. for tumors with propensity for leptomeningeal spread (MEDULLOBLASTOMAS, Ependymomas, CHOROID PLEXUS CARCINOMA, malignant FINEAL REGION TUMORS, spinal MRI must be done!

Cy1 + mural nodule:
1) pilocytic astrocytoma
2) pleomorphic xanthoastrocytoma (PXA)
3) hemangiblastoma
4) gangglioglioma, esp. desmoplastic infantile gangglioglioma / astrocytoma (DIGDHA)
5) metastasis
6) neurocysticercosis

PERFUSION-WEIGHTED MRI (PW-MRI)
markedly increased rCBV - excess vasularization (growth of high-grade tumors); increased rCBV - low-grade tumors; decreased rCBV - vasogenic edema or radiation necrosis.

DIFFUSION-WEIGHTED MRI (DW-MRI)
Tumors show diffusion restriction! (due to hypercellularity and proteineaceous 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 SENSOR IMAGING (DTI-MRI)
- shows tracts in peritumoral area - guides safer tumor resection.

GENERALIZED Q-SAMPLING IMAGING
- can visualize tracts in peritumoral edema even better than DTI.

MRI
- presurgical evaluation of eloquent cortex. see also p. D66 >>

Alternative – intraoperative electrical cortical mapping.

MRS
- noninvasive in vivo method of analyzing tissue chemical spectrogram.
• commonest abnormalities in gliomas (vs. necrosis)
  increased:
  - choline (membrane metabolism)
  - N-acetyl aspartate (living neurologic tissue)
  - choline / creatine (cellu lar bioenergetics).
  - lactate
Brain Tumors (General)

Onc (16)

- decreased – NAA/creatine.
  
  Tumor – lots of membranes (choline↑), no normal neurons (NAA↓), metabolism anaerobic (lactate↑ and creatine↓).

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

Necrosis – only lipids:
  
  no normal neurons (NAA↓), no normal membranes (choline↓), no metabolism (creatinine, lactate)

As comparison – infarction (stroke) region:
  
  decreased - N-acetyl aspartate (NAA↓), creatine↓, choline↑*

*choline is only difference from tumor

Tumor – lots of membranes (choline) and anaerobic metabolism (lactate)

Stroke – everything is down except anaerobic metabolism (lactate)

Necrosis – everything is down except dead lipids

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

Glioblastoma multiforme - elevated choline/creatine (Cho/Cr) ratio, persistent N-acetyl aspartate (NAA) and lipid/lactate peaks:

Radiation necrosis - large lipid/lactate peak with absent choline, creatine, and NAA:

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 H215O.

  - tumors that respond to therapy become hypometabolic (before they shrink in size on MRI).

  - recurrent symptoms after radiation therapy:
    
    a) recurrent / residual tumor (glycolytic activity↑)
    
    b) 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.

**H215O 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 18F-deoxyglucose - region (corresponding to MRI enhancement) has increased metabolism compared with white matter (arrows).

**Angiography** - historical method for diagnosing brain tumors (for many cases MRA suffices).
Current indications:
1. Preoperative assessment of tumour vascularity, mapping of major vessels before biopsy:
   a) tumors that may encircle critical vessels (e.g. basal MENINGIOMAS)
   b) tumors that can be extremely vascular (e.g. HEMANGIOBLASTOMAS, MENINGIOMAS, GLOMUS tumors).
2. Embolization to reduce intraoperative bleeding (e.g. bulky highly vascular MENINGIOMAS - done in temporal proximity (24-96 hours) to planned surgery.
3. Differentiation of intra-axial and extra-axial tumors (if cross-sectional imaging is equivocal).

Angiographic abnormalities:
1. Increased vascularity:
   1) increased number of normal vessels (or accentuated capillary blush)
   2) actual tumor vessels - irregular and tortuous (bizarre), may bear microaneurysms or show AV shunting; may be seen as blush (diffuse stain) during late arterial or capillary phase.
      Most hypervascular tumors - CHOROID PLEXUS PAPILLOMAS, HEMANGIOBLASTOMAS
2. Avascular areas - necrosis or cyst formation.
3. Vascular displacement; may indicate tumor position relative to neuraxis: superficial brain mass will compress vessels against cranial vault or falx cerebri, whereas one outside brain will separate them from these structures; mass within temporal lobe elevates MCA (MCA draped over expanded lobe).
   - may indicate herniation. see p. S54 >>

feeding vessels are clue to tumour origin; cerebral tumors are fed by cerebral vessels, choroid plexus tumors - by choroidal vessels, extracerebral tumors - by meningeal vessels.
Exceptions: MENINGIOMAS - not infrequently acquire pial supply; GLIOMAS and, particularly, METASTASES - dural supply is well documented.
BIOPSY

- definitive tissue diagnosis necessary for adequate treatment planning. see p. D34

  • most primary brain tumors are verified histologically, but 80% metastatic tumors are diagnosed & treated empirically.

  • biopsy is not indicated in CHORDOMA, GLIOMA, AND DIFFUSE BRAIN STEM GLIOMAS
    - characteristic MRI 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.

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 of heterogeneous nature - 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 at herniation, open biopsy is preferable).

Open excision may result in unacceptable functional impairment without positive influence on survival.

There is no indication for craniotomy when purpose is merely to biopsy (and not resect) tumor.

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 plaque or solitary large meningioma

7. Progressive strokes (rare)

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

N.B. immunosuppressed patients are at risk for both primary CNS lymphomas and CNS infections (such as toxoplasmosis at cryptococcosis) - patients treated empirically with antibiotics should undergo prompt biopsy of lesions that are not responding to therapy.

COMPLICATIONS

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

1. tumor seeding to meninges

2. reaction to previous therapy

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

N.B. posterior fossa tumors can cause reverse herniation after ventricular shunt insertion (therefore, drain EVD at 15 cmH2O)

hydrocephalus requiring permanent shunt develops in 60% patients after posterior fossa tumor removal.

INTRATUMOR HEMORRHAGE

- tumors that most often cause hemorrhage (strokelike onset of focal neurologic deficit): 1) glioblastoma multiforme, high-grade astrocytoma

2) some metastatic tumors (melanoma, renal cell carcinoma, choriocarcinoma, testicular carcinomas).

- "menses in brain"

- may be provoked by iatrogenic thrombocytopenia (associated with chemotherapy)

- clinically insignificant = dramatic

- treatment - osmotic agents and glucocorticoids a surgical decompression.