Low Grade Gliomas

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Definition

Four Types of Glial Cells:

- Astrocytes --> Astrocytomas
- Oligodendrocytes ---> Oligodendrogliomas
- Ependymal Cells ---> Ependymomas
- Microglia

Astrocytomas

Definition

Astrocytic tumor/Astrocytoma:

- tumors comprised largely of astrocytic cells
- generic term applied to diffusely infiltrating well differentiated astrocytic cells

Epidemiology

- 50% of all new diagnoses of Brain Tumors are primary tumors of glial origin
  Astrocytomas consititute 25-35% of all gliomas
- Children > Adults (Bimodal Age distribution 6-12 yrs vs. 26-46yrs)
- Correlation between age and tumor grade
  - 40's: Low grade astros
  - 50's: Anaplastic astros
  - 60's: GBM
- 1.5M > 1F
- Locations: Frontal, Temporal, Parietal, uncommon in occipital lobe
- Lobar associated with well circumscribed lesions vs.
  Deep associated with diffusely infiltrating

Grading System

WHO (Kernohan)	Designation	Histologic Criteria (Ste.Anne/Mayo/ Daumas-Duport)
I	Pilocytic	no features
II	Diffuse	nuclear pleomorphism
III	Anaplastic	nuclear pleomorphism and mitoses
IV	Glioblastoma	nuclear pleomorphism, mitosis, microvasc prolif, and/or necrosis

Histologic Classification

WHO (Kernohan)	Cell Type	Histo features
I	Pilocytic Optic Glioma Cerebellar Glioma	microcysts/rosenthal fibers lacy, cystic/rosenthal fibers rosenthal fibers
II	Fibrillary Gemistocytic Protoplasmic	Fibrillary strong GFAP eosinophilic, strong GFAP microcystic/mucoid, weakGFAP
III	Anaplastic	three of: nuclear pleomorphsim, mitosis, vascular proliferation, necrosis

Grades I and II can be challenging Dx: must differentiate from reactive gliosis (inflammation)

Risk Factors

- Familial
- Pre-existing inflammatory lesions
- Exposure
- Trauma

Familial Risk Factors

Associated w/ neuroectodermal syndrome

- Neurofibromatosis -1 (von Recklinghausen) 17q11
  - optic gliomas
  - intracranial gliomas
- Neurofibromatosis -2 (Bilateral Acoustic Neuroma) 22q12
  - neurofibroma
  - meningioma
  - astrocytoma
  - ependymoma
  - schwannoma
- Tuberous Sclerosis (Bourneville's disease -autosomal dominant chromosome 9 or 11)
  - Triad: Developmental Delay/Seizures/angiofibromas (adenoma sebaceum)
  - periventricular hamartomas
  - well differentiated low grade glioma
  - GBM rare
- von-Hippel Lindau (autosomal dominant chromosome 3)
  - hemangioblastoma of cerebellum and retina
  - RCC
  - Phaeo

Not associated w/neuroectodermal syndrome

- predisposition in famalies with glioma
- incidence reported as high as 57/100k vs. 12/100k in general population

Occupational Exposure

Occupational

- Rubber workers
- Petrochemical
- Microwave exposure
- Radiation exposure (Tinea capitis)
- Vinyl Choloride

Chemicals

- polycyclic hydrocarbons
- nitroso compounds
- triazines

Other Risk Factors

Inflammatory lesions and Trauma

- case reports of gliomas arising from MS plaques
- associated with Progressive Multifocal Leukoencphalopathy (JC virus)
- no association w/gliomas and old trauma sites

Hormones

- pregnancy and glioma
  - increased detection from increased peritumoral edema
  - accelerated growth from estrogen?
- Sporadic reports of reduced incidence in Diabetics?

Pathophysiology

- Etiology and Pathogenesis of astrocytomas poorly understood
- Pathophysiology via mass effect and tissue invasion

Gross Pathology

- Ill defined boundries
- Yellow white, homogenous
- Single or multiple cysts
- Diffusely infiltrative leading to distortion of normal structures

Micro Pathology

- Majority of Low grade gliomas are fibrillary.
- Cell density: minimal increase, usually 2x of normal
- Microcystic change a good marker for disease, normal tissue does not become cystic
- Satellitosis: astrocytes cluster around neurons
- Nuclei are pleomorphic. NO MITOSES
- Gemistocytic Astrocytes: eosinophillic, often dedifferentiate into malignant astrocytomas

Clinical Presentation

- Seizures most common presentation
- Symptoms of raised ICP
- Cortical Syndromes
- Focal Neuro Deficit
- Global Neuro Deficit
- Pain
- Endocrine Dysfxn (?common ones)
- Psychiatric

CT/MR

CT:

- non-contrast enhancing lesion
- low density

MR:

- non-contrast enhancing
- hypodense on T1, hyperintense on T2
- well circumscribed

Natural History

Malignant potential

Median survival

- Gr 1 tumors >10yrs
- Gr2 tumors ~5yrs
  - 10yr survival ~20%
  - (most patients pass within 10yrs)

Favorable Prognostic features

- Young age at time of dx
- Lack of major neuro deficit
- Seizures as presenting symptom
- Long duration of symptoms prior to dx

Poor Prognostic Features

- Presence of significant neuro deficit
- Decreased LOC
- Raised ICP

Effects of Surgery

- Cerebellar asrocytomas have excellant prognosis (possible cure)
- Gemistocytic astrocytomas frequently transform post resection

Medical Management

Anticonvulsant Therapy

- Role for prophylactic use unclear
- Sz risk in Un-operated patient
  - Inverse association of Sz frequency and degree of malignancy
    - oligoastrocytoma 81%
    - astrocytoma 66%
    - ependymoma 50%
    - glioblastoma 42%
  - Tumor location also correlates with frequency w/ frontal, parietal, and temproal lesions having periop sz frequencies ~40%
  - Anti-epileptics of choice dilantin vs tegretol
- Sz Risk in Operated patient
  - extent of resection unproven association
  - Decreased sz's post-op seen in
    - elderly
    - women
    - higher grade
    - aggressive resection
  - Increased Sz w/ post-op evidence (48hrs)
    - ICH
    - Cerebral edema
    - Infarction
- Long-term AntiConvulsant use
  - unclear, no good evidence
  - monitor for side-effects
  - 15% of patients on dilantin develop serious side effect warranting d/c

Medical Management

Corticosteroids in Glioma

- Lipophillic hormone that alters gene transcription --> anti-inflammatory and catabolic at physiologic levels
- High dose steroids yield membrane stabilization and reduce brain tumoral edema, mechanism poorly understood
- Popular theory that steroid inhibits glioma synthesis of proteins that make the BBB leaky
- Recently challenged as no change seen in total brain water and BBB integrity studies
- Alternate theory, increased protein and Na driving osmolar forces
- PET studies infer dexamethasone has a vasoconstricting effect

- Perioperative Considerations
  - Continued use in post operative period standard
  - Straight forward resections consider quick taper
  - Subtotal resections w/ symptomatic ICH may be continuted long-term as pallaition
  - Complications
    - cutaneous stigama
    - immunosuppression
    - peptic ulcer
    - psychosis
    - steroid myopathy
    - Cushing's syndrome
  - Remember dilantin increases the plasma clearence of dexamethasone and decreases its bioavailability

Surgical Management

Controversial how best to manage
Indications for Immediate Surgical Tx
- Enhancement on neuroimaging
- Presence of mass effect
- lesion crossing midline
- Papillaedema or focal deficit
- Age > 40

Medical Treatment
- Steroids
- Anti-convulsants

Surgery
- Timing: no good evidence that early surgery improves outcomes
- Extent:
  - no conclusive evidence that extensive resection better than conservative resection
  - aggressive/maximal safe resection = delayed recurrance
- Early biopsy for dx only proven benefit
- Reasonable indications for Sx:
  - Childhood cystic cerebellar astrocytomas
  - Pilocytic astrocytoma
  - Symptomatic ICH 2' to mass effect
  - Hydrocephalus
  - Refractory Sz
  - Well circumscribed lobar tumor

Radiotherapy

Indication, timing and dose of radiation uncertain

Case series suggest radiation lengthens survival

Radiation Protocols vary

- Fractionated therapy 5500cGy x5-6weeks directed at tumor bed and rim of tissue
- Whole brain radiation not usually considered
- Complete vs Incomplete radiation?

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Pilocytic Astrocytoma

Definition

Pilocytic Astrocytoma:

- a morphological distinct group of astrocytomas that occur frequently in the 3rd ventricle

Epidemiology

- Comprise 5-10% of all gliomas
- Age peak 5-15yrs, >80% under 20yrs
- M=F
- Most common primary tumor in children
- Associated w/ NF-1 in 30-50% of cases
- 3rd ventricle most common, uncommon in hemispheres and brainstem

Gross Pathology

- Most commonly found in 3rd ventricle
- Well circumscribed
- Soft gray mass +/- cyst formation

Micro Pathology

Two histologic patterns recognized

- Juvenile (most common)
- Adult

<u>Juvenile Type</u>

- sparsely structured bipolar loosely arranged astrocytes associated w/microcysts
- Rosenthal fibers: glial filaments, fibril rich processes

DDx of Rosenthal fibers:

- cerebellar astrocytoma
- gliosis from mass effect
- Alexander's disease

Adult Type (Bipolar Spongioblastoma)

- Homogeneous sheet
- Firm w/ variable calcification
- microscopic invasion at edges
- Few microcysts, no Rosenthal fibers

Clinical Presentation

- Headache
- Nausea and Vomiting
- Hydrocephalus
- Visual Loss
- Ataxia/Cerbellar signs
- Cranial Nerve palsies (Diplopia)
  (compression in post fossa)

Natural History

- Slow growing, malignant transformation
- Prolonged duration of symptoms before dx
  (~months to years)
- Rarely involute without treatment
- Tumor may spread through subarachnoid space
- Median survival @ 20yrs >70% --> location dependent
  (Thalamic/Hypothalamic invasion common)
- Gross total resection = Cure

CT/MR

CT:

- discrete cystic/solid mass
- >95% enhance
- minimal surrounding edema
- solid componant hypo/iso dense
- calcified lesions (20%) associated w/hemorrhage
- look for hydrocephalus

MR:

- T1 solid portions iso/hypointense
- T2 solid portions hyperintense
- FLAIR cyst contents do not suppress: hyperintense to csf
- MRS: elevated choline, decreased NAA, high lactate

DDx
AnaplasticOligo
Astrocytoma
Ganglioglioma
DNET
PXA
Cerebritis
Ischemia
AVM
Herpes

Treatment and Results

Cerebellar/Hemispheric

- Gross total resection attempted
- Adjuvant chemo given if residual disease present
- 95% cure if gross total

Opticochiasmatic/hypothalamic

- Surgery limited to bx or debulking
- Timing: visual loss
- Radiation and Chemo for disease control
- <5yr survival

Optic Glioma

Definition

Optic Glioma:

- tumor arising from the optic apparatus

Epidemiology

- Uncommon, <1% of Brain tumors
- 75% occur in 1st decade
- Children>Adults
- Associated w/ NF-1 in 30-50%

Classification

Same grading criteria as Astrocytomas

Optic Nerve Gliomas classified by site:

- Optic nerve
- Optic Nerve and Chiasm
- Optic chiasm and hypothalamus

50-85% of optic gliomas will involve the Chiasm or hypothalamus

Gross Pathology

- May be solid or cysitc
- Fuisform shape involving optic nerve expanding it, invades pia and grows along optic sheath
- Lesion is a central core of expanded nerve surrounded by a layer of neoplastic astrocytes
- May involve Chiasm or posterior optic pathway
- Skip lesions seen

Micro Pathology

- Low grade astrocytoma, benign appearence
- Two patterns
  - Lacy, low cellulairty, pilocytic, with cyst formation
  - highly fibrillated cells and rosenthal fibers associated with chiasm optic gliomas
- malignant transformation uncommon

Clinical Presentation

- Progessive visual loss and Seizures
- Visual field defects if chiasm involved
- Proptosis
- Papillaedema, Optic atrophy
- Macrocephaly
- Hypothalamic involvement
  - Diencephalic syndrome
  - DI
  - Anorexia
  - Obesity
  - Hypersomina
  - Precocious puberty

Natural History

- Unpredictable behaviour
- Spontaneous tumor regression and visual clearing have been reported
- Survival >10yrs expected
- Slow progressive visual loss main symptom
- Rarely transform, low malignant potential
- Hypothalamic invasion a poor prognosis

CT/MR

DDx
Lymphoma
Germinoma
Pit adenoma

- Diffuse fusiform enlargement of optic nerve
- Non contrast enhancing low density lesion in suprasellar region
- MR character of low grade glioma
- MR screening of assymptomatic NF-1 children yield a 15% catch rate of optic glioma

Treatment and Results

Conservative

- Anterior/Orbit tumors can be followed w/MRI and visual testing q6mos.
- ~70% will show progression

Surgery

- Case series suggests a gross total resection of optic nerve proper yields
  - 95% cure rate
  - 85% 20yr survival
- Hypothalamic and Chiasmatic tumros should all be biopsed to exclude differential diagnosis
- CSF shunting if hydrocephalus develops

Radiation and Chemo

- mixed opinions
- aggressive treatment in children with progression coutnered with effects of radiation on brain
- radiation @ 5200-5600CGry shown to imrpove tumor control and stabilize visual loss w/ increased risk of development of astrocytoma, moya moya
- Chemo w/Vincristine & actinomycin D showed inhibition of tumor growth w/ delay in radio tx

Olidodendrogliomas

Definition

Oligodendroglioma:

- uncertain cell of origin
- thought to arise from oligodendrocytes or immature precursor
- well differentiated, slow growing
- diffusely infiltrating cortical/subcortical

Epidemiology

- Oligodendrogliomas account for 5-25% of all gliomas
- Adults>Children (Age distribution 26-46yrs)
- CSF Metastases are rare
- Spinal cord primary oligodendrocytes uncommon (2.6% on intramudllary tumors)
- May be multifocal or multicentric
- Preferred sites Frontal>>>Parietal >Temproal> Cerebellum>brainstem>spinal cord
- Predilection for white hemispheric matter

Gross Pathology

- Appear to arise from white matter
- Gelatinous to soft grey/pink
- Sometimes discrete masses
- Occasional grittiness due to Ca2+
- Hemorrhage not uncommon

Micro Pathology

- Characteristic nuclei have rounded "fried egg" appearence on permanant section
- Difficult to dx on frozen section as cells do not have characteristic appearence
- Monotouns sheets
- Infilitrative into pia and cortex -->satellitosis around neurons
- Vascularity often seen does not indicate malignancy
- Calcospherites: microscopic calcification seen in 73% cases
- GFAP negative
- Percentage of tumors have componant of astrocytoma --> mixed gliomas. Mixed gliomas with cysts associated w/ slightly better prognosis
-

Clinical Presentation

- Headache (78%)
- Seizure (70%)
- Paralysis (50%)
- Visual loss
- Papillaedema
- Dementia
- Ataxia
- Nausea
- Abnormal Reflexes
- Hemorrhage

Average age of symptoms before diagnosis ~5yrs

CT/MR

CT:

- mixed density
- calcified lesion (70-90%)
- cystic degeneration (20%)
- may erode calvaria
- hemorrhage and edema uncommon

MR:

- 50% contrast enhance
- hypo to iso dense on T1, hyperintense on T2
- well circumscribed with minimal edema
- MRS: elevated choline, decreased NAA

DDx

AnaplasticOligo
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Herpes

Natural History

Malignant potential

Local Recurrence and CSF seeding Common

Median survival =10yrs, 5yr survival rate= 50-75%

Presence of astrocytic component does not affect prognosis

Favorable Prognostic features

- Young age at time of dx
- Frontal location
- Lack of enhancement
- Loss of 1p and 19q --> more chemosensitive

Poor Prognostic Features

- Malignant features (cellularity, mitosis, vascularity)

Effects of Surgery

- Complete resection improves survival
- no association w/transformation post subtotal resection
- Oligos are chemosensitive --> procarbazine, CCNU, and cincristine
- Unclear wheter radiosurgery is an effective adjunct

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