Maybe It’s A Tumor?! – Common Pediatric Brain Tumors

Pediatric Grand Rounds
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October 12, 2012

Disclosure

• I have no relationships with commercial companies to disclose.

Learning Objectives

• Understand the clinical presentation, diagnostic work-up, and standard treatments of a child with a brain tumor.
• Be aware of some of the common brain tumors found in children.
• Be familiar with the late effects from treatment that can effect a child with a brain tumor.

Case

• 8yo female presents to her PCP with several day history of
  – Headache
  – Vomiting
  – Dizziness
  – Subjective Fever

Chances It’s A Tumor

• ~3000-3500 new cases of brain tumors diagnosed in the US yearly
• Gastroenteritis is the 2nd most common infection diagnosed in the US
Why This Topic Is Important

- Brain tumors are the 2nd most common cancer in children, after leukemia
- Most common solid tumors in children
- Overall 5 year survival = 60-70%

Differences Between Adult and Pediatric Brain Tumors

- See more low grade lesions
- Majority of lesions are infratentorial

Age Distribution

Tumor Location

Brain Tumor Classification

- WHO Classification
- Histologic Classification
- Anatomic Classification

WHO Classification

- Tumors of Neuroepithelial Tissue
- Germ Cell Tumors
- Tumors of the Sellar Region
Histologic Classification

- Histologic Classification
  - Neuroglial Cells
    - Astrocytes
    - Oligodendrocytes
    - Ependyma
    - Choroid Plexus
  - Neuronal/Embryonal Cells

Anatomic Classification

- Cerebrum
- Cerebellum
- Pineal Region

Clinical Presentation

- Increased intracranial pressure
- Localizing signs/symptoms
- General signs/symptoms

Clinical Presentation: Increased Intracranial Pressure

- Headache
- Vomiting
- Irritability
- Lethargy
- Papilledema
- Separation of sutures, bulging fontanelle
- Head tilt
- Anisocoria
- Ataxia
- Parinaud syndrome: failure of upward gaze

Clinical Presentation: Localizing Signs and Symptoms

- Based on tumor location
- Abnormal eye findings: visual loss, head tilt, nystagmus, diplopia
- Cranial nerve palsies
- Ataxia
- Hemiparesis
- Hemisensory loss
- Early handedness or change in handedness
- Seizures
Clinical Presentation: General Signs and Symptoms

- Headache
- Vomiting
- Developmental delay
- Weight loss or gain
- Failure to thrive
- Endocrine abnormalities
- Behavioral changes

Initial Work-up

- Full exam with focus on neurologic exam to include vision
- CT scan
- MRI brain and spine
- CSF examination
- Blood and CSF for tumor markers

Treatment

- Surgery
- Radiation
- Chemotherapy

Surgery

- Usually needed to establish diagnosis
- Total resection is most ideal when feasible
  - Usually unable to biopsy deep brainstem lesions
- May need VP shunt for obstructive hydrocephalus
- Acute side effects: neurologic deficits
Radiation
• Can be used for all brain tumors with minimal exceptions
• Full treatment dose: 5400 – 5940 cGy
• Prophylaxis dose: 1800 – 3600 cGy
• Acute side effects: nausea, vomiting, fatigue, skin changes, hair loss

Chemotherapy
• Adjuvant therapy in most cases
• In young children (< 3 yrs), attempt to use as first line to avoid radiation because of long term neurocognitive sequelae
• Blood brain barrier thought to limit use, however with higher doses, in particular high dose chemotherapy with autologous stem cell rescue, able to overcome this
• Acute side effects: nausea, vomiting, myelosuppression, infection, hair loss, mucositis, neuropathy, changes in taste

Common Pediatric Brain Tumors
• Medulloblastoma
• Ependymomas
• Brain stem tumors
• Astrocytomas
• Optic Glioma
• Intracranial Germ Cell Tumors
• Craniopharyngiomas
• Atypical Teratoid Rhabdoid Tumor (AT/RT)

Medulloblastoma
• AKA Cerebellar PNET
• Most common malignant brain tumor in children
• Small round blue cell tumor
• Location: Posterior fossa
• Common Presentation:
  – Signs and symptoms of increased ICP
  – Ataxia
  – Cranial nerve palsies, esp 6th
• Staging:
  – MRI brain and spine
  – CSF examination
  – Bone marrow &/or bone scan – only if symptomatic

Imaging

Pathology
www.emedicine.medscape.com
Medulloblastoma

- Risk Categories:

<table>
<thead>
<tr>
<th>Extent of Resection</th>
<th>Standard Risk</th>
<th>High Risk</th>
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<tr>
<td>Residual tumor &lt; 1.5 cm³</td>
<td>&lt; 1.5 cm³</td>
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<td>Histology</td>
<td>Anaplasia</td>
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</tr>
<tr>
<td>Age at Dx</td>
<td>&gt; 3yrs</td>
<td>&lt; 3yrs</td>
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</tbody>
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- Desmoplastic variant

Medulloblastoma

- Treatment for Standard Risk:
  - Gross total resection (GTR) when possible
  - Radiation is a must (except < 3 yrs)
  - Adjuvant chemotherapy with cisplatin/CCNU/vincristine or cisplatin/cytoxan/vincristine

- High risk: resection, radiation, aggressive chemotherapy to include autologous stem cell rescue

- Prognosis:
  - Standard risk: 80-85% event free survival (EFS)
  - High risk: 20-70% EFS

Ependymomas

- 9% of all primary childhood CNS tumors
- Can occur in the spinal cord
- Common Presentation:
  - Increased ICP
  - Ataxia
- Common Location: 4th ventricle
- Staging:
  - MRI brain/spine
  - CSF examination

Ependymomas

- Treatment:
  - GTR when possible
  - Radiation: tumor is very responsive
  - Chemotherapy: no advantage to adjuvant therapy shown
    - Possibility of 2nd-look surgery following 2 courses of chemo if GTR not achieved

- Prognosis:
  - 50-70% EFS for completely resected non-metastatic tumors
  - Poor prognosis for metastatic tumors
**WHO Classification of Astrocytomas**

- **Grade I**, pilocytic astrocytoma: fibrillary background, rare mitoses, classically Rosenthal fibers, well circumscribed and slow growth, usually behaves in benign fashion
- **Grade II**, diffuse or fibrillary astrocytoma: more cellular and infiltrative and more likely to undergo anaplastic change
- **Grade III**, anaplastic astrocytoma (AA): highly cellular with significant cellular atypia, locally invasive and aggressive
- **Grade IV**, glioblastoma multiforme (GBM): increased nuclear anaplasia, pseudopalisading and multinucleated giant cells

**Astrocytomas**

- **Low-grade (I/II)**
  - Most common pediatric brain tumor
  - Location: can occur anywhere in the brain
  - Presentation: Depends on where occurs
  - Staging: MRI brain +/- spine

- **High-grade (III/IV)**
  - Presentation: Variable depending location
  - Seizures (if supratentorial)
  - Staging: MRI brain +/- spine

**Imaging**

- **Low-grade**
- **High-grade**

**Pathology**

- **Low-grade**
- **High-grade**

**Astrocytomas**

- **Low-grade**
  - **Treatment:**
    - GTR
    - Chemotherapy = carboplatin and vincristine
    - Radiation = used when chemo fails
  - **Prognosis:**
    - Excellent (approaching 100%) when GTR

- **High-grade**
  - **Treatment:**
    - GTR = often not possible because can cross midline and very infiltrative
    - Chemotherapy = with or without radiation
  - **Prognosis:**
    - For AA with GTR and adjuvant therapy EFS ~85%
    - For GBM, EFS < 10%

**Brain Stem Tumors**

- 15-20% of all childhood CNS tumors
- Any brain tumor histology can occur in the brain stem
- Diffuse Intrinsic Pontine Gliomas (DIPG) vs. Low-Grade Astrocytoma of Brain Stem (NF-1, tectal lesions)
- **Common Presentation:**
  - Brain stem findings (diplopia, slurred speech, facial droop)
  - Increased ICP
  - Temp instability, trouble swallowing secretions, resp. issues
- **Staging:**
  - MRI brain only
Brain Stem Tumors

- **Treatment:**
  - Surgery, to include biopsy, usually not feasible
  - Radiation – while not curative can prolong tumor progression for 3-12 months
  - Chemotherapy – limited data to suggest advantage, often use temozolomide in combination with radiation

- **Prognosis:**
  - DIPG – 2 yr survival rate < 10-20%
  - Low-grade astrocytoma of brain stem – 2 yr survival 60% or more (bright enhancement on post-contrast MRI and often in areas of brain stem besides pons, i.e. exophytic)

Optic Glioma

- 5% of primary CNS tumors in childhood
- Neurofibromatosis present in up to 70% of patients with these tumors
- Common Presentation:
  - Loss of vision
  - Proptosis
  - Asymmetric nystagmus
- **Treatment:**
  - Biopsy can compromise vision; reserved for extension into optic canal or increasing visual compromise
  - Radiation – may help preserve vision
  - Chemotherapy – Carboplatin and vincristine as in low-grade astrocytomas
- Can have an indolent course so decision to treat should be based on if there is disease progression on imaging or if visual compromise

Craniopharyngiomas

- 6-9% of childhood CNS tumors
- Can involve the pituitary
- Slow growing
- Presentation:
  - Increased ICP
  - Visual loss
  - Endocrine dysfunction
- **Treatment:**
  - Complete excision when possible
  - Radiation – when incomplete resection, addition decreases relapse and improves long-term survival
  - Chemotherapy – no role
- **Prognosis:**
  - 5 yr EFS 80-90% with complete resection
  - With subtotal resection, relapse rate 50%
  - Life-long endocrine dysfunction if present at diagnosis
Intracranial Germ Cell Tumors

- 1-3% of primary pediatric CNS tumors
- Multiple tumor types seen:
  - Germinomas (~55%)
  - Non-germinomatous germ cell tumors (NG-GCT)
  - Teratomas and mixed germ cell tumors (~33%)
  - Others: malignant endodermal sinus tumors, embryonal cell carcinomas, choriocarcinomas, teratocarcinomas (~10%)
- In all but germinomas, serum and CSF alpha-fetoprotein (AFP) and βHCG may be elevated

Germinoma

- Presentation:
  - Suprasellar – panhypopituitarism, DI
  - Pineal region – raised ICP, Parinauds syndrome
  - 10% multifocal
- Staging:
  - MRI brain/spine
  - CSF for tumor markers (AFP, βHCG neg)
- Treatment:
  - Radiation (whole ventricular, craniospinal)
  - +/- Neoadjuvant chemotherapy with radiation dose based on response
- Prognosis:
  - > 80%
  - Endocrine abnormalities will not resolve with successful treatment

NG-GCT

- Presentation:
  - Precocious puberty
  - DI
  - Panhypopituitarism
  - Raised ICP
- Staging:
  - MRI brain/spine
  - CSF for tumor markers
  - No biopsy if markers positive
- Treatment:
  - Neoadjuvant chemotherapy followed by response based radiation (includes craniospinal)
- Prognosis:
  - 40-70%
  - Can follow tumor markers to assess response

Imaging

Germinoma

NG-GCT

Pathology

Germinoma

NG-GCT

Atypical Teratoid Rhabdoid Tumor (AT/RT)

- Very aggressive tumors often seen in children < 3 yrs
- Often mistaken for medulloblastoma
  - Pathologically similar except INI-1 negative
- Fatal if treated with medulloblastoma therapy but survival approaches 50% if treated with high-dose chemotherapy with autologous stem-cell rescue
IN1-1 Staining

www.emedicine.medscape.com

Brain Tumors in Children < 3 yrs

• Worse prognosis
• Higher risk for neurotoxicity:
  – Mental retardation
  – Growth failure
  – Leukoencephalopathy
• Attempt to avoid or delay radiation

Genetic Associations

• Neurofibromatosis-1 (NF-1) – optic pathway gliomas, other gliomas, meningiomas
• Tuberous sclerosis – gliomas, ependymomas
• Retinoblastoma – at risk for trilateral disease with pineoblastoma
• Li-Fraumeni (p53) – choroid plexus tumors, astrocytomas
• Von Hippel-Lindau syndrome – cerebellar hemangioblastoma
• Turcot’s syndrome – gliomas
• Gorlin’s syndrome – medulloblastoma

Late Effects of Treatment

• Complications related to treatment that persist or arise once cancer therapy is completed
• Can affect quality and quantity of life
• Most survivors will experience at least 1 late effect
• Many influencing factors such as age, gender, tumor type, treatment received, ability to cope and degree of support
• Psychosocial effects such as anxiety, depression, school & employment issues can occur with any treatment

Brain Surgery Late Effects

• Depends on location of tumor and degree of resection
• Impairment of neurological function

“Late effects represent the price that was paid for cure and the quality of life that was purchased.”

- Jan van Eys
Cranial Radiation Late Effects

- Neurodevelopmental effects
- Second malignancies (meningiomas, high grade gliomas, melanomas)
- Abnormal growth and maturation
- Endocrine abnormalities
  - GH Deficiency
  - Hypothyroidism
- Vision Problems
- Hearing loss

Brain Tumor Chemotherapy Late Effects

- Neurodevelopmental effects
- Second malignancies
- Hearing loss
- Kidney damage
- Infertility
- Abnormal growth and maturation
- Endocrine abnormalities

Endocrine Late Effects

- There are endocrine abnormalities that the patient may present with or develop during treatment and those that develop much later secondary to treatment
  - DI on presentation in a patient with a CNS germinoma vs. hypothyroidism 8-10 years following cranial radiation
- Any damage to the hypothalamic-pituitary axis secondary to the tumor seen on presentation or that develops during treatment is not reversible and the patient will need life-long hormone replacement
  - Suprasellar tumors

Summary

- Brain tumors are the 2nd most common cancer seen in children
- Overall survival is 60-70% and with newer treatments will continue to improve
- More survivors = more late effects

References

- www.emedicine.medscape.com
- www.childrensoncologygroup.org
- www.survivorshipguidelines.org