

Viewing Time

The program will take up to one hour to complete.

Target Audience

This program is designed for primary care physicians.

Other health care professionals working with patients and their families may also find this program of interest.

Faculty Disclosure

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Faculty Disclosure

Anne Bendel, M.D. has disclosed no actual or potential conflict of interest in relation to this educational activity.

During this educational activity **Dr. Bendel** will not be discussing the use of any commercial or investigational product not approved for any purpose by the FDA.

Pediatric Central Nervous System Tumors

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Pediatric Central Nervous System Tumors

A lecture about the etiology and treatment of pediatric brain tumors

Program Objectives

Upon completion of this program, participants should be able to:

- Discuss comprehensive care for pediatric brain tumor patients
- Understand current theories on pediatric brain tumor etiology
- Describe advances in treating pediatric brain tumors

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Receiving CME Credit

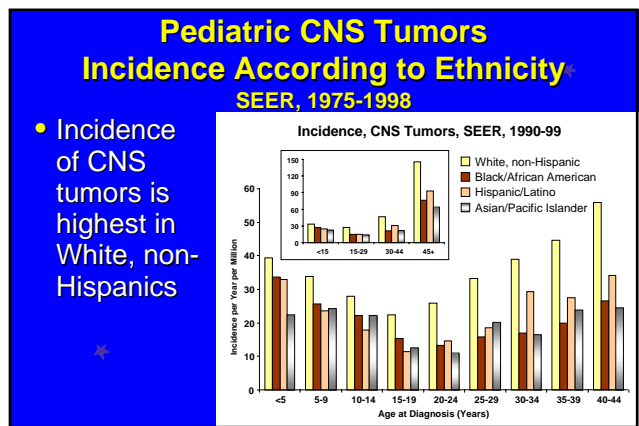
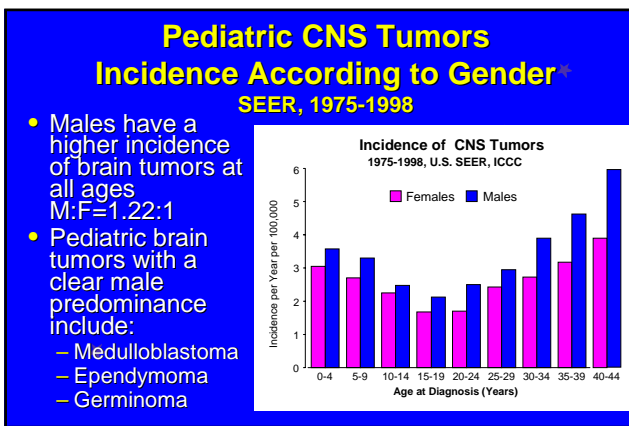
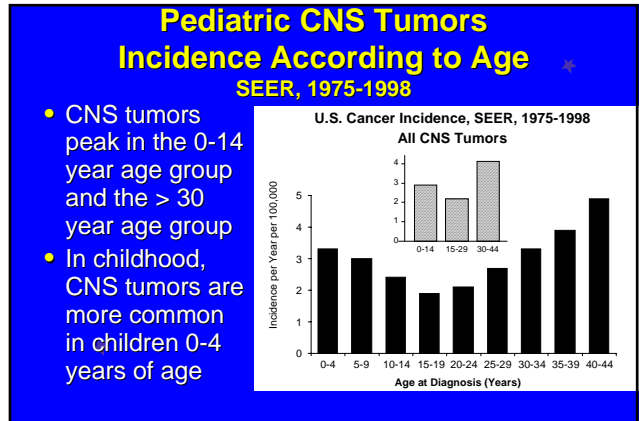
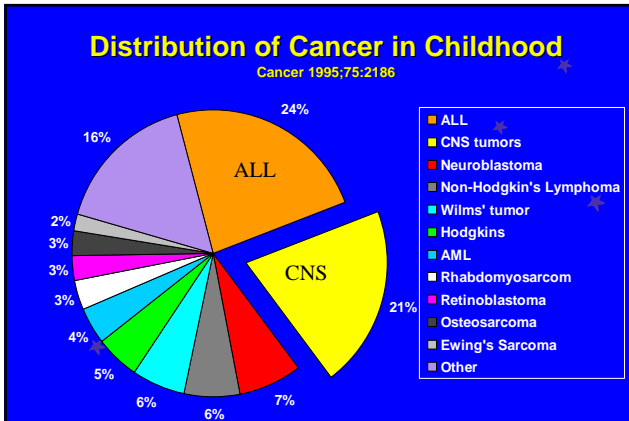
To receive CME credit you must view the entire program and complete the evaluation form at the end.

Pediatric Central Nervous System Tumors

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Grand Rounds, May 20 & 22, 2008

Pediatric Central Nervous System Tumors (CNS) Incidence

- CNS tumors are the second most common childhood cancer, making up 21% of all pediatric cancers.
- 2200 children (< 20 years of age) are newly diagnosed with a CNS tumor each year in the USA for an incidence rate of 3.5 per 100,000 children. [SEER]
- "CNS Tumors" include malignant and benign tumors of the brain and spine. Spinal cord tumors are rare in children accounting for only 4-6% of CNS Tumors.
- CNS tumors cover a wide array of different tumor types



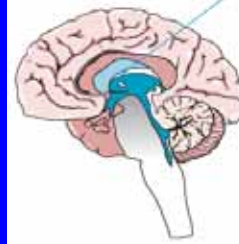
- ### Conditions / Agents Associated with Brain Tumors in Children
- Inherited genetic syndromes with mutation of a tumor suppressor gene
 - Neurofibromatosis-1
 - Neurofibromatosis-2
 - Tuberous Sclerosis
 - Von Hippel Landau
 - Li Fraumini (p53)
 - Retinoblastoma gene
 - Familial Adenomatous Polyposis (Turcot's)
 - INI1 gene: ATRT/Rhabdoid
 - Prior CNS radiation

- ### Agents NOT associated with Brain Tumors in Children
- Perinatal ultrasound
 - Stalberg K et al: *British Journal of Cancer* (2008) **98**, 1285-1287.

Pediatric CNS Tumors Signs and Symptoms

- Dependent on the site of tumor, age of child, and aggressiveness of the tumor
- Due to:
 - the effect of the tumor or peri-tumoral edema on the surrounding brain.
 - obstructive hydrocephalus resulting early morning headache, vomiting, lethargy
- Symptoms in babies may be vague due to their inability to communicate and the fact that their skulls can expand

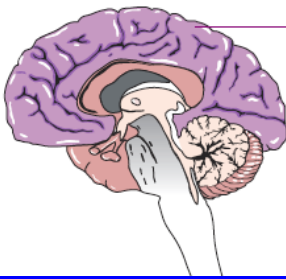
Central Tumors Signs & Symptoms



- Headache* 49%
- Abnormal eye movements and squint 21%
- Nausea and vomiting* 19%
- Papilloedema* 18%
- Reduced visual acuity 16%
- Unspecified symptoms and signs of raised ICP* 13%
- Diabetes insipidus 12%
- Abnormal gait and coordination difficulties 10%
- Optic atrophy 9%
- Behavioural change or school difficulties 9%
- Altered level of consciousness 9%
- Reduced visual fields 8%
- Seizures 7%
- Hemiplegia 7%
- Focal motor deficit 7%
- Developmental delay 7%
- Short stature 7%
- Weight loss 5%
- Vertigo or auditory symptoms 5%
- Visual or eye abnormalities (unspecified) 5%

Supratentorial Tumors Signs & Symptoms

Wilne S et al: Lancet Oncol. 2007 Aug;8(8):685-95



- Supratentorial tumours:**
- Unspecified symptoms of raised ICP* 47%
 - Seizures 38%
 - Papilloedema* 21%
 - Focal neurological signs 17%
 - Headache* 11%
 - Hemiplegia 10%
 - Nausea and vomiting* 8%
 - Macrocephaly* 6%

Posterior Fossa Tumors Signs & Symptoms



- Nausea and vomiting* 75%
- Headache* 67%
- Abnormal gait and coordination difficulties 60%
- Papilloedema* 34%
- Abnormal eye movements 20%
- Lethargy 13%
- Nausea without vomiting* 10%
- Unspecified symptoms and signs of raised ICP* 9%
- Weight loss 9%
- Focal motor weakness 9%
- Macrocephaly* 7%
- Impaired consciousness 7%
- Vertigo or auditory symptoms 7%
- Squint 6%
- Stiff neck 6%
- Head tilt
- Accidental head injury 5%

Brain Stem Tumors Signs & Symptoms



- Brain stem tumours:**
- Abnormal gait and coordination difficulties 78%
 - Cranial nerve palsies (unspecified) 52%
 - Pyramidal signs (unspecified) 33%
 - Headache* 23%
 - Squint 19%
 - Focal motor weakness 19%
 - Facial palsy 15%
 - Papilloedema* 13%
 - Unspecified symptoms of raised ICP* 10%
 - Abnormal eye movements 6%
 - Behavioural change or school difficulties 5%

Spinal Cord Tumors Signs & Symptoms



- Spinal cord tumours:**
- Back pain 67%
 - Abnormal gait or coordination difficulties 42%
 - Spinal deformity 39%
 - Focal motor weakness 21%
 - Sphincter disturbance 20%
 - Decreased upper limb movement 17%
 - Developmental delay 8%
 - Head tilt 7%
 - Headache* 7%

Pediatric CNS Tumors: Diagnostic Studies

- Pre-operative
 - CT of head (unenhanced), to assess for hydrocephalus and calcification
 - MRI of head with contrast
 - ?MRI of spine with contrast to look for metastasis
 - ? CSF analysis to assess for:
 - Cytospin for malignant cells
 - Germ cell tumor markers (α FP, β HCG)
 - ? Angiogram to assess vascularity
 - Possible pre-op embolization to reduce risk of bleeding
 - ? Functional MRI to assess critical areas
- Surgical Resection or Biopsy to make a diagnosis
 - ?Use of motor strip grid to assess critical areas during resection
 - ?Use of intra-operative MRI to assess degree of resection

Historical Development of Therapy for Brain Tumors

- Surgery (1910's - Cushing)
- Radiation (1910's - Nordentoft)
 - Chemotherapy (1960's)
- Immunotherapy/Vaccination (1990's)
 - Targeted Therapy (2000's)

Pediatric CNS Tumors General Principles of Treatment

- Goal is to eradicate the tumor with minimal long term neurological deficits
- Most tumors are locally aggressive therefore good local control with surgery with or without radiation therapy is necessary
- Some tumors spread through the CSF therefore whole brain and spine radiation and/or chemotherapy are needed to control disease
- Spread outside the CNS is rare

Surgery

- Almost all CNS tumors need at least a biopsy to make the diagnosis—the exceptions are optic tract tumors and diffuse brain stem tumors, and some germ cell tumors.
- Complete resection is the goal, with completeness of resection as the most important prognostic factor in almost all brain tumors.
- Surgical mortality is less than 1%
- Morbidity dependent on site of tumor, preoperative neurological condition and extent of resection

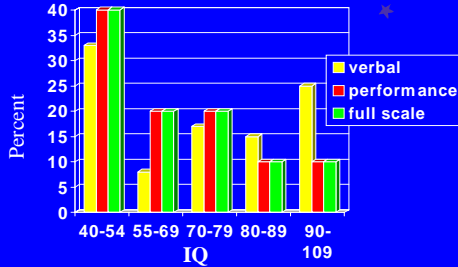
Radiation Therapy

- Radiation improves prognosis in the majority of brain tumors
- As dose of radiation is increased the effectiveness is increased—but toxicity is also increases
- New advances in radiation technology have resulted in more precise radiation to the target and thus decreased toxicity to the normal brain
- Radiation to the tumor bed is often used for local control
- Radiation to the whole brain and spine is often used in tumors with tendency for CSF spread

Radiation Therapy

- Long term sequelae include:
 - intellectual impairment
 - memory impairment (IQ), slow processing speed, attention deficits
 - endocrine dysfunction
 - hearing loss
 - cataracts
 - secondary cancer
- Long term intellectual sequelae can be devastating and are greatest in the young child and are proportional to dose of radiation and size of field irradiated
- Current studies attempt to omit, delay or decrease dose of radiation in the very young child

IQ in children receiving cranial radiation at age < 2 years (n=13)



Int J Rad Oncol Biol Phys 1981;7:727

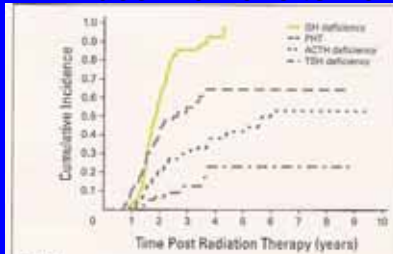
Neuropsychologic Function after Cranial Spinal XRT

- POG 8631 / CCG 923
- Patients with Medulloblastoma
- 23.4 vs. 36 Gy XRT
- Data for younger group only (<9 years)
- Reduced dose radiation decreases the long term cognitive effects.

| | Standard XRT (n=6) | Reduced XRT (n=5) |
|-----------------|--------------------|-------------------|
| Verbal IQ | 76.0 | 87.0 |
| Perf IQ | 69.0 | 83.0 |
| FS IQ | 70.0 | 85.0 |
| Attention Index | 72.5 | 88.0 |
| FS IQ Change | -22.5 | -12.0 |

Mulhern et al, JCO 1998

Endocrine Deficits from Radiation



Laughton SJ et al: J Clin Oncol. 2008 Mar 1;26(7):1112-8

Patients with embryonal brain tumors received Craniospinal radiation (median dose 2340cGy n=53, 3960cGy n=35), Pituitary/Hypothalamic radiation (median dose 3860-3980cGy n=53, 4970-5050cGy n=35)

Fig 2. Cumulative incidence of specific endocrine deficits following radiation therapy. GH, growth hormone; PHT, primary hypothyroidism; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone.

Chemotherapy

- Improves survival in some tumors
- Allows for a reduced dose of radiation in other tumors
- In babies chemotherapy can help delay or omit the need for radiation
- Possible Sequelae
 - Acute
 - nausea
 - pancytopenia
 - alopecia
 - peripheral neuropathy
 - anorexia and weight loss
 - fatigue
 - Delayed
 - decreased hearing
 - renal dysfunction
 - infertility
 - secondary leukemia

Immunotherapy

- Passive (targeted monoclonal antibodies)
 - Radiolabeled monoclonal antibodies (radiation emitting)
 - Immunotoxins (toxin linked to antibody)
- Adoptive (cellular therapy)
 - Introduction of cultured autologous or allogeneic immune cells such as lymphokine activated killer cells (LAK) or cytotoxic T lymphocytes (CTL's) into the tumor.
- Active (tumor vaccines)
 - Intradermal antigen pulsed autologous dendritic cell vaccines (DCVax).
 - Viral infected tumor vaccines.
 - CMV vaccine for high-grade glioma

Brain Tumor Stem Cells

- There is evidence that a minority cell population with stem cell properties (self renewal & differentiation) are responsible for the maintenance and growth of brain and other tumors.
- These cells are widely present in fetal brain and small numbers persist in the adult.
- Committed neural cells may convert into cancer stem cells by mutations and/or changes in the environment.
- In neural tumors, stem cells have been detected in glioblastoma, medulloblastoma and ependymoma.

Targeting Cancer Stem Cells

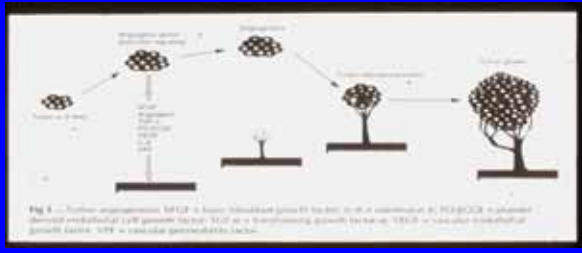
- These stem cells may be difficult to eliminate due to chemotherapy resistance.
- The cancer stem cell hypothesis implies these cells are a critical target.
- Stem cell genes and signaling pathways are novel targets for cancer therapy.
- A problem inherent in the use of drugs affecting stem cell gene functions is that normal stem cells can be targeted together with cancer stem cells.

Brain Tumor Stem Cell Targets

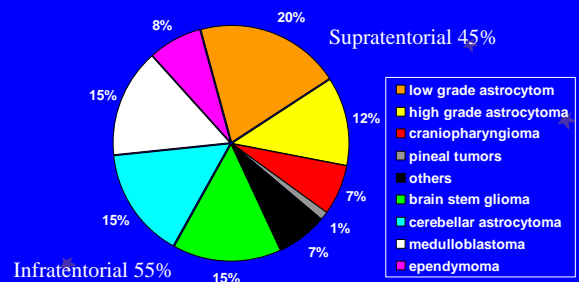
- **Embryonic Development Genes**
 - "Sonic Hedgehog" (SHH) in Medulloblastoma
 - Notch in Astrocytoma
- **Stem Cell Maintenance Genes**
 - Bmi1 in Medulloblastoma and Astrocytoma
- **Cell Growth Regulators**
 - PTEN in Medulloblastoma and Astrocytoma
 - mTOR inhibitors (mTOR "down stream" of PTEN)
 - Sirolimus (Rapamycin), temsirolimus (Torisel®), everolimus (RAD001)
 - EGFR inhibitors (EGFR "up-stream" of PTEN)
 - erlotinib (Tarceva®), gefitinib (Iressa®)
- **Tumor vasculature**
 - Angiogenesis inhibitors
 - Bevacizumab (Avastin®)

Anti-angiogenesis

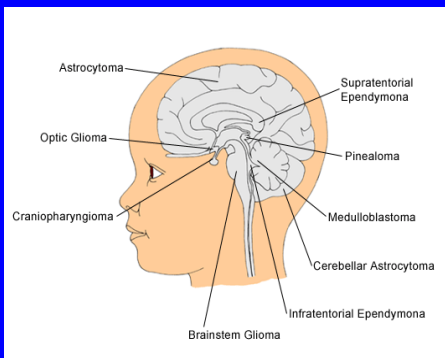
- Angiogenesis is the formation of new blood vessels.
 - Tumors up to 2mm in size can get nutrients by passive diffusion, therefore to grow any larger new blood vessels must be created
- Antiangiogenic agents work by blocking new vessel growth



Distribution of Pediatric Brain Tumors



Pediatric CNS Tumors—Location



Pediatric CNS Tumors Astrocytoma (Glioma)

- Comprise > 50 % of all pediatric CNS tumors
- Originate from the astrocyte or glial cell—makes up the supportive tissue in the brain
- Usually classified as "low grade" or "high grade"
- Low grade gliomas are a tumor of childhood, high grade gliomas are more common in teens and adults
- Symptoms and length of symptoms are dependent on location and grade of the tumor
- **Common locations:**
 - Cerebellum (24%)
 - Brain stem (24%)
 - Optic tract
 - Hypothalamus/thalamus
 - Cerebral cortex
 - Spinal cord

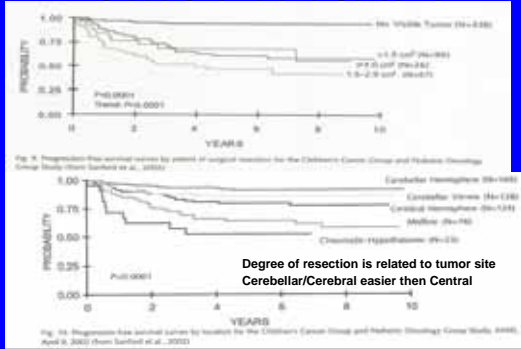
Pediatric CNS Tumors Astrocytoma (Glioma)

- WHO grading system (histologic)
 - WHO I = pilocytic astrocytoma (JPA)
 - WHO II = fibrillary or diffuse astrocytoma
 - WHO III = anaplastic astrocytoma
 - WHO IV = glioblastoma multiforme
- WHO grade correlates with the invasiveness or aggressiveness of the tumor and prognosis
- WHO I/II are termed "low grade gliomas"
- WHO III/IV are "high grade gliomas"

Low Grade (WHO I/II) Astrocytoma

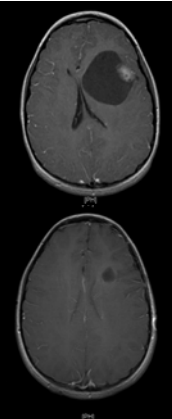
- Comprises > 80% of all pediatric astrocytomas
- Typically remains localized
- Surgical resection is initial treatment and most important prognostic factor. Location of tumor determines ability for complete resection
- Complete resection—10 yr. survival of 95-100%
- Incomplete resection
 - 10 yr survival of 89% for WHO I
 - 10 yr survival of 80% for WHO II
- May have years of quiescence or a course of waxing and waning
- Radiation or chemotherapy may improve survival for recurrence or progression

Surgical Resection and Location of Low Grade Glioma and Outcome



Low Grade Glioma

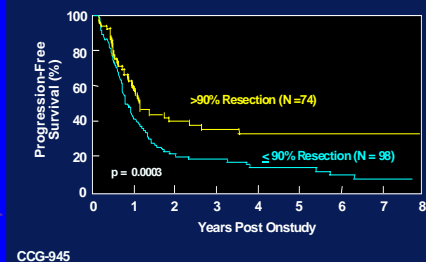
- 12 year old girl with a several month history of headaches, drop off in school performance, and new onset seizure
- MRI showed a large cyst with an associated solid nodule
- She underwent a complete resection of the lesion
- Pathology showed a WHO I (low grade) glioma
- She is 10 years from diagnosis with no evidence of disease and no neurological sequelae



High Grade Glioma (WHO III/IV)

- Usually in a supratentorial location
- Typically remain localized, only rarely spreads via CSF
- Complete resection with local radiation and chemotherapy is the treatment of choice
- WHO III (Anaplastic Astrocytoma)
 - 10 yr. survival of 35-45%
- WHO IV (Glioblastoma Multiforme)
 - 10 yr. survival of 20%

Amount of Residual Disease Is Associated with Outcome in Children with High-Grade Glioma

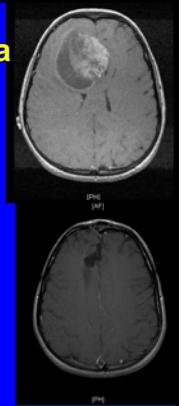


Molecular Genetics - Astrocytomas

- Genetic alterations that accompany the childhood high-grade astrocytic neoplasms are distinct from those that occur in adults.
 - EGFR amplification is common in adults, rare in children.
 - PTEN mutation is common in adults, rare in children.
- Inactivation of the TP53 tumor suppressor gene is seen in more than 95% of older children with malignant astrocytomas.
 - Mutations of TP53 are seldom seen in malignant astrocytoma of children younger than 3 years.

High Grade Glioma

- 17 year old with several week history of headaches
- MRI showed a right frontal lobe enhancing lesion with surrounding edema
- She underwent complete resection, focal radiation and chemotherapy
- 2 years later she began having seizures and was found to have a local recurrence
- She underwent a complete resection of the recurrent tumor with the use of the intra-operative MRI
- She is presently undergoing chemotherapy



Brain Stem Glioma

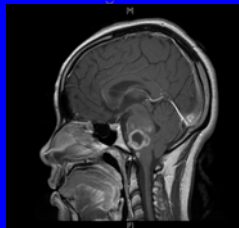
- Comprise 15% of childhood CNS tumors
- 70% are diffusely infiltrating and involve the pons—"Diffuse Pontine Glioma"
- 30% are focal and/or exophytic and involve other areas of the brain stem

Diffuse Pontine Glioma

- Comprises 70% of all brainstem tumors in children
- Symptoms are usually < 6 weeks in duration and consist of cranial nerve and long tract findings
- Uniform histology—astrocytoma with high grade features
- Surgery not indicated due to high risk of morbidity
- Local radiation improves symptoms and survival
- Chemotherapy has never been shown to improve outlook
- 5 year survival of < 10%
- Median length of survival 9-13 months
- Needs new innovative therapy

Diffuse Pontine Glioma

- 15 year old female with a 2 week history of face and tongue numbness, diplopia, ataxia, left sided weakness
- MRI showed a Diffuse Pontine Glioma
- No surgery performed
- Treated with focal radiation
- Initial improvement in symptoms
- Died of progressive disease 5 months from diagnosis

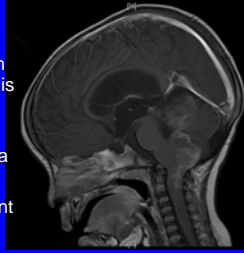


Focal or Exophytic Brainstem Glioma

- Occurs in 30% of brainstem gliomas
- Symptoms have often been present for months
- Typical histology is low grade astrocytoma
- Complete surgical resection is the goal
- Radiation or chemotherapy may improve survival
- 5 yr. survival of 50-60%

Focal/Exophytic Medullary Astrocytoma

- 2 year old boy presented with a 4 month history of ataxia, self-induced injury to his right face, and right weakness
- MRI showed exophytic brainstem glioma
- Partial debulking of exophytic component showed JPA
- Patient started on chemotherapy
- 16 months after diagnosis—tumor stable and symptoms improved



Medulloblastoma/PNET

- Second most common type of CNS tumor in children
 - 20% of CNS tumors
- Peak incidence 4-9 years, M:F=1.7:1
- Highly malignant—categorized as high risk vs low risk
- High tendency for leptomeningeal spread
- Medulloblastoma
 - Arises from the cerebellum
 - Good prognostic factors: no metastases, complete resection, age greater than 3 years, favorable histology, trkC expression, low c-myc and erbB2 expression
- Primitive Neuroectodermal Tumor (PNET)
 - Arises from a location other than the cerebellum (cerebral cortex, pineal)
 - All PNET classified as high risk

Medulloblastoma/PNET

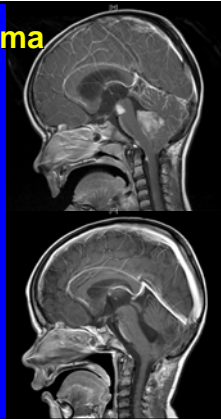
- Treatment—dependent on risk factors
 - All patients undergo attempt at complete resection and chemotherapy
 - Most patients receive radiation to the tumor bed and craniospinal axis
 - Dose of radiation dependent on age, presence of metastases, and histology
 - Craniospinal radiation is delayed or omitted in children younger than 3 years of age
- Low risk medulloblastoma—5 yr. survival of 75-85%
- High risk medulloblastoma/PNET—5 yr. survival of 65%
- New studies are looking at stratifying treatment based on other biological factors (Trkc, cmyc, erbB2)

Molecular Genetics - Medulloblastoma

- Medulloblastoma is molecularly distinct from the supratentorial primitive neuroectodermal tumors
- “Sonic Hedgehog”(SHH), “Wingless” (WNT/WG), and ERBB are medulloblastoma developmental signaling pathways.
 - Cyclopamine is a plant teratogen that cause cyclopia in sheep fetuses and inhibits a member of SHH.
 - Less toxic derivatives of cyclopamine being evaluated in medulloblastoma.
 - Erlotinib (Tarceva®) inhibits ERBB1 (EGFR) & ERBB2 (HER/neu) signaling in human medulloblastoma cells and may have therapeutic potential.

Medulloblastoma

- 5 year old with few week history of irritability, and 2-3 day history of vomiting, lethargy and ataxia
- MRI showed a posterior fossa tumor with metastatic disease and hydrocephalus
- Treated with complete resection; radiation to whole brain and spine (3600 cGy) and tumor bed (5400 cGy); chemotherapy
- Patient alive 2 years from diagnosis
- Long term issues with hearing loss, growth hormone deficiency, hypothyroidism and moderate cognitive impairment



Ependymoma

- 8% of brain tumors
- Originate from the ependymal cells lining the ventricles
- 4th ventricle is the most common site, but 3rd and lateral ventricle and the spinal cord are other sites
- Rarely with leptomeningeal spread
- M:F=1.9:1
- Peak incidence/location
 - 2-6 years of age
 - intracranial tumors
 - 4th ventricle
 - adolescence
 - spinal cord
- Good prognostic factors include: site other than 4th ventricle, complete resection, no metastases, non-anaplastic

Ependymoma

- Treatment dependent on location, extent of resection and histology
 - All patients require an attempt at complete resection
 - Chemotherapy is indicated in patients with bulky residual disease
 - All patients require radiation to the tumor bed (except for completely resected non-anaplastic supratentorial or spinal cord ependymoma)
- Prognosis
 - Complete resection ~60-80% long term survival
 - Incomplete resection ~20-40% long term survival

Molecular Genetics – Ependymoma

- Ependymomas occurring at different sites demonstrated distinct genetic signatures and arise from restricted populations of radial glia stem cells.
- Pediatric posterior fossa ependymomas appear to have a molecular signature distinct from their adult counterparts which occur in the spine and cerebrum.
- Thus, ependymomas should be treated with therapies that target the abnormal cell signal pathways and not based on histology or location.

Ependymoma

- 5 year old male with a 4 month history of early morning vomiting, headache, ataxia, diplopia
- An MRI showed a posterior fossa mass
- Complete resection was performed
- Post-operative complications included swallowing dysfunction, bilateral 6th nerve weakness, deafness in right ear, ataxia and dysmetria
- Pathology consistent with an ependymoma
- He received focal radiation
- He is 5 years s/p diagnosis with no evidence of disease, persistent right 6th nerve weakness, deafness in right ear, ataxia, right sided dysmetria

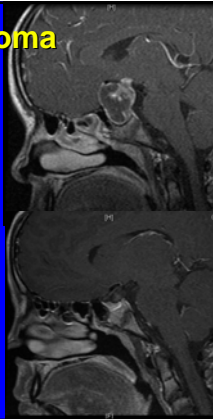


Craniopharyngioma

- 3-5% of brain tumors
- Occurs at any age
- "Benign"
- Associated with DI and other hormonal dysfunction
- Treatment
 - Surgery and/or radiation
- Prognosis—>80% long term survival
- Long term issues with pan-hypopituitary, obesity, visual impairment

Craniopharyngioma

- 9 year old girl presented with failure to thrive and was found to be growth hormone deficient, to have partial DI, and to have a bilateral temporal visual field cut
- MRI showed a large cystic calcified tumor in her sella and suprasellar area
- She underwent complete resection and the pathology was consistent with a craniopharyngioma
- She is 5 years from diagnosis and has no sign of disease
- She has panhypopituitarism, hypothalamic obesity and excessive daytime sleepiness

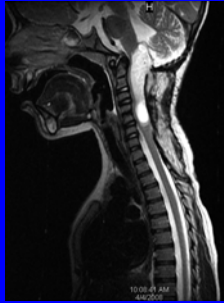


Spinal Cord Tumors

- Account for 4-6% of Childhood CNS Tumors
- Surgical resection is typically all that is needed unless high grade or progressive
- Astrocytomas make up 60-80%
 - Intramedullary
 - 75% cervical or thoracic, 20% distal cord, 5% filum terminale
 - More common in the younger child
 - Typically low grade
 - 10 year survival is 80-85% if complete resection
- 20-40% are ependymomas
 - Most often located in cervical cord, the next most common location is the filum terminale where myxopapillary ependymoma typically arise.
 - More common in older children and adults
 - 10 year survival of 90% if complete resection

Cervical Cord Astrocytoma

- 18 month old girl who presented with delayed gross motor skills and a preference to tilt chin/head upward
- Physical exam showed moderate quadraparesis
- Underwent a complete resection with pathology showing a Grade I Astrocytoma.
- Unfortunately she has had 2 recurrences and is now receiving chemotherapy



Pediatric CNS Tumors - Summary

- Overall survival of CNS Tumors is 55-65% compared to > 75% survival for all childhood cancers combined
- Survival for CNS tumors are slowly improving due to collaborative efforts through the Children's Oncology Group and others
- Poorer survival in CNS Tumors is secondary to:
 - delayed diagnosis
 - risk of surgery and radiation injuring the normal brain
 - the blood brain barrier which limits penetration of chemotherapy into the brain
- Morbidity exceeds that of other malignancies because of the neurological deficits associated with the tumor and its treatment
- Challenges are to find new surgical and radiation techniques that spare normal brain and to develop therapy that targets brain tumor stem cells or has improved penetration into the brain

Bibliography

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Information Resources

- Genetics Home Reference <http://ghr.nlm.nih.gov>
- Clinical Trials www.clinicaltrials.gov
- Noteworthy Treatments www.vim.edu/ncmh
- New approaches to brain tumor therapy www.nabtt.org
- American Brain Tumor Association www.abta.org
- National Brain Tumor Foundation <http://braintumors.org>
- The Brain Tumor Society www.tbs.org
- Accelerate Brain Cancer Cure <http://abc2.org>
- Surgery www.neurosurgery.ucla.edu
- Dendritic Cell Vaccine Trials www.nwbia.com

Question

Is there an increasing incidence of brain tumors over time?

Question

Is there an association of CMV with brain tumors?

Question

Do we know the mechanism of action that explains why radiation is so effective with brain tumors?

Question

How can we more selectively apply neuro-imaging to children who have first seizures so we get an early diagnosis of brain tumors without having to image every child who has a seizure?

Question

Question about counseling and following patients after radiation therapy in terms of their risk for endocrine dysfunction

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