Optic Pathway Gliomas are Neoplasms!

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Nothing to disclose
Optic Nerve Glioma
"When something is shouted loudly enough, often enough, and to enough people, with no checking of the accuracy of what's being shouted, a downright silly claim can come to sound like a long-suppressed truth."

S. Beckwith, Phila. Inq. 10/28/11
Optic pathway glioma are neoplasms!

- Claim that OPGs are hamartomas not requiring treatment, even if progressive
  - Hoyt and Baghdassarian (1969), Parsa
- Today a better understanding of the growth patterns and clinical behavior of OPGs
  - MRI’s visualization of brain and visual pathways
  - Careful serial follow-up by dedicated pediatric ophthalmic/neuro-ophthalmic specialists working together with pediatric neuro-oncologists
Optic pathway glioma are neoplasms!

- Growth patterns are varied and are unpredictable
  - Many are benign and can be observed
  - Some clearly act aggressively

- Are OPGs hamartomas or slowly growly neoplasms?
Hamartoma vs. Neoplasm

- **Hamartoma**
  - Benign, focal malformation
  - Tissue elements normally found at that site, but disorganized
  - Grows at the same rate as surrounding tissue
  - Most often asymptomatic
  - Often found incidentally at autopsy
Hamartoma vs. Neoplasm

- **Neoplasm**
  - A mass caused by an abnormal proliferation of cells
  - Growth uncoordinated w/ surrounding normal tissue
  - Histologically may be benign or malignant
  - May grow at different rates
  - Varying potential for metastases
1. Optic pathway gliomas do not satisfy the definition of hamartomas

- Local destruction and invasion
  - Can destroy structures within and around which they are growing
1. Optic pathway gliomas do not satisfy the definition of hamartomas

- **Growth rates**
  - At times can be more rapid than that of the visual pathways or brain
1. Optic pathway gliomas do not satisfy the definition of hamartomas

- Can be symptomatic
  - 50% of NF/OPG have vision loss to some degree (Balcer AJO 2001)
  - Endocrinopathy
    - Precocious puberty
    - Russell’s diencephalic syndrome
1. Optic pathway gliomas do not satisfy the definition of hamartomas

- Can metastasize (without a shunt)
2. Histopathologically, OPGs are neoplasms

- **WHO grade I juvenile pilocytic astrocytomas**
  - Just like childhood cerebellar JPA’s

- **Some OPGs are gr. II fibrillary astrocytomas**
  - Distinction is artificial
  - Many, particularly in NF1, are not biopsied
OPGs can be Grade I or II astrocytomas

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<td><strong>Total (12)</strong></td>
<td><strong>286</strong></td>
<td><strong>178 (62%)</strong></td>
<td><strong>54 (19%)</strong></td>
<td><strong>3 (1%)</strong></td>
<td><strong>45 (16%)</strong></td>
<td><strong>6 (2%)</strong></td>
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Optic nerve enlargement due to a glioma, with tumor in the nerve and outside the nerve (lower portion)
Optic nerve replaced by glioma (top).
Glioma spread to adjacent region (lower part)
2. Histopathologically, OPGs are neoplasms

- Lack of malignant transformation does not make OPGs hamartomas
  - Craniopharyngiomas
  - Subependymal giant cell astrocytomas
2. Histopathologically, OPGs are neoplasms

- OPGs may exhibit markers of cellular proliferation (Walrath 2008, Miller 2008)
  - +AgNOR (silver nuclear organizing region)
    - Measure of mitotic activity
  - +MIB-1 (antibody to Ki-67 antigen)
    - Like pilocytic astrocytomas in other brain locations, some OPGs have elevated proliferative activity (MIB-1 labeling index of 2-3%), which is associated with more aggressive tumor behavior
    - Don’t generally see apoptosis in low grade tumors
3. Biologically, OPGs are neoplasms

**Neurofibromin**

- RAS
  - Raf
    - MEK
    - MAPK
  - PI3K
    - Akt
    - mTOR

Cell Division and Survival

Slide courtesy of Dr. Lucy Rorke-Adams
4. Spontaneous improvement and resolution can be seen in neoplasms

- OPGs (Liu and Lessell 1992)
- Neuroblastomas
  - Of 53 six month infants found to have NB on screening, 17 (32%) had complete spontaneous regression (Tanaka 2010)
  - Can also occur in stage IV NB with metastases
    - Highly malignant - < 40% cure rates
Stage 4S Neuroblastoma - Spont. Regression

3 months

10 months

Courtesy of Kate Matthay, MD, UCSF
Anti-mitotic therapies for OPGs work!

- **Radiation**
  - 10-year progression-free survival rates 66%-90%
    - PFS = tumor growth less than 25%
  - No longer used first line because of side effects
Anti-mitotic therapies for OPGs work!

- **Chemotherapy**
  - When clinical (visual) progression documented
  - Vincristine/carboplatin well tolerated by children
  - Radiology as the primary outcome measure
    - 69-77% prog.-free surv. at 3-5 years (Packer 1997, Ater 2008)
  - Vision (NF1/OPG) as the primary outcome measure
    - Meta-analysis (Moreno 2010): Imp. 14% + Stable 47% = 61%
    - Multicenter, retrospective (Fisher 2010, n=115, 10 sites): Imp 32% + Stable 40% = 72%
  - There will be no trial comparing CTX vs. no CTX
Other therapies for OPGs

- **Molecularely targeted agents**
  - Inhibitors of BRAF, MEK, and mTOR are being tested in clinical trials for low grade gliomas

- **Angiogenesis inhibitors**
  - Bevacuzimab
Deleterious mindset: designating OPGs as hamartomas

- Disservice to and potentially dangerous for patients with OPGs and their families to call them hamartomas not requiring treatment.
- Some are life threatening!
- Families may get the false impression that if treatments are ineffective or unnecessary, clinical f/u and imaging are also unnecessary.
OPGs are truly neoplasms!

- **Not hamartomas**
  - Occasional aggressive growth patterns
  - Histopathology (grade I or II), + tumor markers

- **Spontaneous improvement**
  - Can be seen in highly malignant neoplasms

- **Use treatments appropriate for neoplasms**
  - Clinical progression: vincristine and carboplatin
  - More directed therapies will be used in the future