Advances In Orbital Neuropathology

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Overview

• Non-neoplastic lesions
  – Microphthalmos/pseudoglioma
  – Cephaloceles
  – Neuroma

• Tumors
  – Neurofibroma
  – Schwannoma
  – Meningioma
  – Optic Nerve Glioma

• Genetic advances in Pilocytic Astrocytoma
The ophthalmic artery and nasociliary nerve enter the orbit intraconally and, wrapping around the lateral aspect of the optic nerve, travel to the medial wall where they both give off their ethmoidal branches.
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• Genetic advances in Pilocytic Astrocytoma
Microphthalmia

- Caused by incomplete closure of fetal cleft
- Usually unilateral
- Often with large cyst
- May be associated with chromosomal deletions (13q or 18)
- Eye can be relatively normal or totally disorganized.
- Proliferating neuroectodermal tissue in the cyst can simulate neoplasm (pseudogliomatous hyperplasia)
Microphthalmia with cyst
Cephaloceles

- Developmental malformations with brain or meninges present in orbit.
- Sometimes retain communication with brain, but this often closes.

- **Meningocele** – only meninges
- **Encephalocele** – only brain
- **Meningoencephalocele** – both present
Amputation Neuroma

- Rare
- Haphazardly entangled regenerating nerve fibers growing from end of disrupted peripheral ciliary nerve(s)
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• Genetic advances in Pilocytic Astrocytoma
Neurofibroma

- Sporadic or NF1 associated
- Localized, diffuse and plexiform types
- Usually arise from sensory nerves
- 6 of 1,264 (<1%) of orbital lesions (Shields)
- Localized lesions can be well circumscribed, but are not encapsulated
- Treatment is surgical excision; recurrence is frequent with larger lesions
Neurofibroma
Plexiform Neurofibroma
Schwannoma (Neurilemoma)

- Often arise from trigeminal nerves; less often from ocular motor nerves
- 14 of 1,264 (1%) of orbital lesions (Shields). Presentation at 10-85 years of age (median 37)
- Mostly sporadic, but can be NF2-associated
- Encapsulated, and can sometimes be separated from the nerve
Schwannoma

Slow progression of proptosis (several years)
Schwannoma
Cystic Schwannoma

Dr. PS Rosenbaum EOPS 2003
Schwannoma

In contrast to neurofibroma and meningioma, schwannomas tend to “roll” along the slide and do not smear well. They also have distinctive elongated nuclei.
Orbital Meningioma

- Can be derived from optic nerve sheath (primary) or extend into the orbit from the brain (secondary)
- 29 of 1264 (2%) of cases in one orbital tumor series were primary optic nerve menigiomas (Shields)
- In the same series, 24 (2%) were secondary intraorbital meningiomas
- Primary tumors unilateral in 95% of cases; bilateral cases usually in young adults
- Primary tumors may be localized or extend along much of orbital-canalicular optic nerve length
Diffuse Process with “Tram-Tracking”

Dr. N Miller
Primary ONSMs usually not surgically curable unless accompanied by removal of optic nerve
Review of Johns Hopkins Cases 1968-2008 (Jain et al)

• 51 cases (21 Primary, 30 secondary)
• Mean age 45 years; 5 in children
• 2 patients with NF2
• 25 Meningothelial, 23 Transitional, 2 Angiomatous 1 Chordoid,
• 4 WHO grade II (elevated mitotic activity, brain invasion, Chordoid subtype)
Mitotic Activity In Grade II Tumor
Invasion of Lacrimal Gland and Muscle
Invasion of Optic Nerve

Equivalent to brain invasion?

Probably not
Chordoid Intraorbital Mengioma (Secondary)
Meningioma Frozen Section Diagnosis

Menigiomas smear easily and have crisp nuclear outlines with delicate chromatin

Dr. P Burger
Optic Nerve Gliomas

- Almost all Pilocytic Astrocytomas
- 48 of 1,284 (4%) of orbital lesions (Shields)
- Can arise from orbital, optic canal or intracranial portions of the nerve
- Most in children in first decade of life
- 25% or more have evidence of neurofibromatosis type 1 (can be bilateral)
- 15% of children with NF 1 have ONGs
Anterior Orbital Presentation:
Proptosis and optic disc swelling
Posterior Orbital/Canalicular Presentation

- Decreased vision (variable)
- No (minimal) proptosis
- Relative afferent pupillary defect

Asymptomatic

- Found during screening for NF1
- Found during evaluation for pale disc
CT scans showing diffuse enlargement of optic nerve
MRI Showing Intracranial Extension
Diffuse involvement of optic nerve parenchyma

N. Miller
Subarachnoid Proliferation of Tumor
Eosinophilic Granular Body (EGB)
Natural History of PA

- Treatment generally not required
- Most remain stable throughout life and do not produce progressive visual loss
- Some spontaneously regress, often with improvement in visual function
- Rare cases increase in size associated with worsening vision
- Sporadic (non-NF1) tumors generally arise earlier and are more likely to grow
- Virtually no risk of spontaneous malignant transformation
Pilomyxoid Astrocytoma

- WHO grade II entity that is clinically more aggressive than Pilocytic Astrocytoma
- Frequently involves hypothalamus/chiasm
- Relatively monomorphous cells with mucoid background
- Perivascular orientation
- No Rosenthal fibers or EGBs
Malignant Optic Nerve Glioma

- 55 year old man
- Presented with visual Sx
- Chiasmal/optic nerve mass
- Died within 1 year of intracranial spread.
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• Genetic advances in Pilocytic Astrocytoma
BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomias


SHORT COMMUNICATION

High-resolution, dual-platform aCGH analysis reveals frequent HIPK2 amplification and increased expression in pilocytic astrocytomias

H Deshmukh, TH Yeh, J Yu, MK Sharma, A Perry, JR Leonard, MA Watson, DH Gutmann and R Nagarajan
Frequent Gains at Chromosome 7q34 Involving BRAF in Pilocytic Astrocytoma

Eli E. Bar, PhD, Alex Lin, MS, Tarik Tihan, MD, PhD, Peter C. Burger, MD, and Charles G. Eberhart, MD, PhD
17 of 25 PA had 7q34 gains

3 cases had activating BRAF mutations (V600E)
Activation of BRAF/MEK/ERK Signaling in Pilocytic Astrocytoma

Bar et al, JNEN 2008

81%
The BRAF gene dupliiction/amplification forms a fusion gene with unregulated kinase activity

Prediction telomeric end of 7q34 gain

KIA
Tandem Duplication Producing a Novel Oncogenic BRAF Fusion Gene Defines the Majority of Pilocytic Astrocytomas

David T.W. Jones, Sylvia Kocialkowski, Lu Liu, Danita M. Pearson, L. Magnus Bäcklund, Koichi Ichimura, and V. Peter Collins

A

B

C

D

KIAA1549 (144kb)

BRAF (190kb)

~2Mb

Duplication

KIAA1549

BRAF 3': KIAA1549 5'

KIAA1549 Ex1-16

BRAF Ex9-18

KIAA1549 Ex1-15

BRAF Ex9-18

KIAA1549 Ex16

BRAF Ex9

KIAA1549 Ex11

BRAF Ex11

KIAA1549 Ex15

BRAF Ex9

20 cases

710bp, 536bp, 392bp

5247bp, 1749aa

1158bp, 386aa

2 cases

5247bp, 1749aa

984bp, 328aa

7 cases

4929bp, 1643aa

1158bp, 386aa

L PA48 PA28 PA49 PA25 NB -ve

600

200
We have identified BRAF/KIA fusion transcripts in all PA with 7q34 gains.

Sample 23
Ras/Raf Signaling Can Be Activated At Multiple Points In PA

Bar et al, JNEN 2008