Proptosis in Optic Pathway Gliomas associated with NF1: Response to chemotherapy

Research conducted with Dr. Grant Liu, CHOP Neuro-Ophthalmology

CNST Luncheon Seminar
Student Summer Research Presentation
October 5, 2012
By the end of this talk, you should be able to...

- Understand neurofibromatosis type 1 (NF1) and its diagnostic criteria
- Evaluate risks of optic pathway gliomas (OPGs)
- Measure proptosis using magnetic resonance imaging (MRI)
- Understand how proptosis index can indicate chemotherapeutic response
- Understand how treatment of NF1/OPG requires collaboration across multiple fields
- Utilize the resources offered by CNST to find your dream summer project and/or funding!
Background
What is Neurofibromatosis Type 1 (NF1)?

* Genetic disorder affecting children starting at birth
  * Autosomal dominant
  * ~50% of cases are de novo
* Increases risk for developing tumors, especially of the nervous system
* Tumors slow growing but can cause damage by compressing nerves
At least 2 out of 7 criteria:

* Café-au-lait spots
* Neurofibromas
* Freckling
* Optic pathway glioma
* Lisch nodules
* Bony lesion
* Family history of NF1
Optic Pathway Gliomas in NF-1

* Young age of onset
  * Commonly arise before age 8
  * Only rarely in older children
* Incidence
  * Found in 15-25% of patients with NF1
* Intrinsic “growths” of the anterior visual pathway
  * Growth patterns unpredictable
Complications of NF1/OPG

- Slow-growing but can cause neural and visual deficits
- Prognosis depends on location
- Visual acuity or visual field loss
- Optic disk swelling or pallor
- Intraorbital: proptosis, strabismus
  - If left untreated, can result in corneal dryness and damage
Treatment Options

* Only for clinically and radiographically progressive OPG
  * Visual acuity loss (60%)
  * Progressive proptosis (10%)
* Chemotherapy is treatment of choice
* Surgical resection only for malignant growth or painful proptosis in a blind eye
  * Universally contraindicated for vision preservation
* Operative risks: paralytic strabismus and ptosis
Basis of current study

- Large retrospective review of NF1/OPG with chemotherapy
- ~Half with proptosis showed subjective improvement
- Proposed proptosis index as alternative to measure chemo response
- Drawbacks: small study, no measurement of tumor volume

Fisher et al., 2012
Diaz et al., 2008
Methods
Retrospective chart review

* Patient records selected from Fisher et al., 2012 review
  * With proptosis before start of therapy
* Collected clinical data about proptosis progression and MRI data
  * Anticipated n=20 (current: n=11)
* Radiographic measurements blind to clinical outcomes
Radiographic Measurement of Proptosis

* Measurements followed established radiographic methodology
  * Correlate well to clinical evaluation (Hertel’s exophthalometry)
* T1 weighted orbital studies
* Orbits 3-D rotated to align
  * Horizontally through mid-lens section
  * Longitudinally through pituitary stalk and fourth ventricle
* Measurements verified by neuroradiologist
Measurement of Proptosis

a = unaffected eye
b = affected eye
c = intrazygomatic line

proptosis degree = b – a

proptosis index = (b - a) post-treatment / (b - a) pre-treatment

* Proptosis index <1 indicates a decrease following treatment; proptosis index >1 indicates increase
Measurement of Tumor Volume

- T2 weighted images
- Calculated tumor margins by signal intensity threshold
- Region of interest (ROI) adjusted by eye to capture portion of tumor in intra-orbital region
- Volumes pre- and post-therapy were compared
Results
Change in Proptosis Following Therapy

Pre-therapy proptosis = 2.78mm
Post-therapy proptosis = 1.78mm

→ Proptosis Index = 0.64 (36% shrinkage)
Change in Proptosis and Volume

Mean Percent Change

Proptosis Index

Volume Index
Proptosis and volume change show no correlation

$R^2 = 0.039$
Results

* Mean proptosis index of 0.54 (n=11)
  * 56% improvement with chemotherapy
  * All subjects showed decreased proptosis
* Mean volumetric index of 0.77 (n=10)
  * 23% shrinkage with therapy
  * Subjects showed decreased tumor volume or no change
* Proptosis index and volumetric change did not show correlation
Discussion
Conclusions

* Confirmed quantitatively in a larger cohort that chemotherapy improves proptosis
  * Radiographic measurements easier to obtain than clinical evaluation requiring specialized skillset
* Proptosis improvement does not predict tumor shrinkage
  * Proptosis and volume should be evaluated as independent measures
Measurements difficult to standardize because of variations in image acquisition protocol
- Slice thickness variability
- Orbital vs. full brain MRI
- Film vs. digital images
  - Inconsistencies in comparing film to digital images
- Pre-therapy data from after start of therapy in several subjects
  - Therapy effect may be underestimated
Next Steps

* Not all data in yet!
  * Anticipate nine more subjects from three institutions
  * Continue analysis as more sites contribute data
* Inter-observer reliability for volumetric measurements
* Correlate to clinical assessments of proptosis
* Consider contribution of tumor size and involvement extra-orbitally
  * May see increased predictive value with gliomas confined to intra-orbital space
The Process

What it’s like to conduct summer research at CHOP
Division of Time

- Shadowing
- Proptosis Project
- Other Research Projects
- Clinical Projects
- Develop Analysis Tools
Cool things I learned this summer:
* Collaboration is key
  * Neuro-ophthalmology, neuro-oncology and neuro-radiology collaborate every day to determine when to treat and treatment options for patients with NF1
  * All research in the field similarly collaborative
  * See November 16, 2012 CNST talk
* Working on multiple projects at once allows you to stay busy and engaged
* Independent research = working at your own pace (and in your own space!)

What I wish I’d known:
* Lots of different IRBs and departmental training– plan ahead!
* Getting data from other institutions is like pulling teeth
Taking advantage of CNST resources

* Determining a field of interest
  * Ask Dr. Hamilton or Dr. Siegel for help, whether you know exactly what you want or have no idea what you’re interested in
* Finding a good mentor
  * Match your interests, but also your working style
* Searching for funding
  * Apply for CNST funding
  * Extramural funding (CNST can help with that too!)
* See announcement for Summer 2013 research
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Thanks!

* Dr. Grant Liu, Neuro-Ophthalmology
* Dr. Michael Fisher, CHOP Neuro-Oncology
* Dr. Tamara Feygin, CHOP Neuro-Radiology

* Dr. Marc Levin
* Dmitry Khrichenko
* CHOP Radiology staff

* American Academy of Neurology Medical Student Summer Research Scholarship
* Dr. Siegel, Dr. Hamilton and the rest of CNST