Drug toxicity surveillance in children

Julius Oatts, MD
University of California San Francisco

4-month-old referred for nystagmus

**RIGHT EYE**
Closed funnel retinal detachment,
Dysplastic retina, vascular stalk centrally
Optic nerve obscured by retinal detachment

**LEFT EYE**
Retinal blood vessels straightened, pulled temporally
Slightly dysplastic optic nerve
Peripheral retinal nonperfusion seen 360°

**Assessment and Plan**

- 4-month-old child with bilateral peripheral retinal vasculopathy
  - Right eye: complete retinal detachment, poor prognosis
  - Left eye: peripheral vasculopathy and optic nerve dysplasia
- Proceed with prophylactic laser photocoagulation, left eye
- TORCH workup, MRI
- Refer to genetics for further workup
Clinical Course

- MRI Brain: Abnormal periventricular white matter and mild diffuse cerebral parenchymal loss
- New developmental delay and autism
- Diagnosed with infantile spasms, started on vigabatrin
- EyeGene testing negative for FEVR variant
- Found to have heterozygous mutation in the NR2E3 gene (c.265 A>G, p. Met89Val)

Repeat EUA with ERG

Left eye only:
- Reduced rod-mediated responses
- Reduced mixed rod and cone-mediated a-wave and b-waves
- Severely reduced oscillatory responses

Summary and Clinical Course

- 2-year-old with developmental delay, autism, infantile spasms on vigabatrin, retinal dystrophy, and genetic variant of uncertain significance presenting with an abnormal ERG after starting vigabatrin
- Vigabatrin discontinued at age 3
- Repeat ERG (age 5) was normal
• 1,281 assessments of 284 children (mean age, 2.09 years)

• Two children (0.7%) had definite vigabatrin-related ocular toxicity

### Vigabatrin

**Clinical concern:** concentric peripheral VF loss  
**Recommended dose:** 50-100 mg/kg/day  
**Baseline exam (prior to initiating):** complete eye exam, visual field testing  
**Follow-up exam:** ideally every 3 months*  
  • Serial fundus exams (thinning of nasal RNFL, macular RPE changes), OCT, visual field testing  

*Most children on vigabatrin are young, nonverbal, and unable to cooperate with examination and/or visual field testing

(Adapted from AAPOS Vigabatrin: The Problem of Monitoring for Peripheral Vision Loss in Children 2017)

### Hydroxychloroquine

**Clinical concern:** toxic maculopathy  
**Early manifestations:** paracentral relative scotomas  
**Recommended dose:** daily max 5.0 mg/kg real weight  
**Baseline exam (within 1 year of initiating):** VA, Amsler grid, ODF  
  • Consider color vision (pseudo-isochromatic plates), SD-OCT, HVF (10-2), fundus photo depending on level of concern  
**Follow-up exam:** SD-OCT, HVF (+/- FAF, mfERG)  
  • Annual screening after 5 years on acceptable dose  
  • Increase risk in patients w/ renal disease or on tamoxifen (consider dose adjustment or more frequent screening)  

(Adapted from AAO Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy - 2016)
Ethambutol

Clinical concern: toxic optic neuropathy
Early manifestations: loss of visual acuity or color vision, central scotoma

Baseline exam: VA, color vision, DFE/optic nerve exam, VF
Monthly exams for dose >15mg/kg/day
(No standard for frequency of exams with doses <15mg/kg/day)

*Consider OCT RNFL or contrast sensitivity testing

Adapted from AAO Drug-Related Adverse Effects of Clinical Importance to the Ophthalmologist (2014)

Panel discussion

• Do you currently screen for Vigabatrin toxicity?
• What are the indications for Vigabatrin screening?
• What diagnostics do you perform, if any?

Panel Discussion

• How do you handle referrals for medications with potential ocular side effects? Does this change for clinical trial patients?
• How do you define clinically significant toxicity?
• How do these principles apply to other medications such as MEK inhibitors or hydroxychloroquine?
• Adult versus child diagnostics: What works and what doesn’t?
## Take home points

- Screening diagnostics and schedules based on adult patients may not apply to children

- Assessment of toxicity is not without risk and ultimately may not change management