Preventing Visual Handicap in Children with Tuberous Sclerosis Complex

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PUBLIC ABSTRACT

Up to 90% of children and infants with tuberous sclerosis complex (TSC) develop seizures and epilepsy. Vigabatrin has become the standard treatment for infantile spasms in Canada, UK, and Europe. Although not officially approved by the Food and Drug Administration, vigabatrin is used in an increasing number of TSC children in New York and throughout USA. Unfortunately, vigabatrin is toxic to the light-sensing photoreceptor neurons, and patients taking the drug frequently experience loss of peripheral vision. Moreover, the visual loss is irreversible even after treatment discontinuation. Despite its retinal toxicity, vigabatrin is a highly effective anticonvulsant, and to preserve cognitive development, vigabatrin monotherapy remains the physician's first-line treatment for children with TSC.

Permanent visual loss from vigabatrin treatment most likely results from the drug's toxicity on photoreceptor and/or inner retinal cell viability. There are two major classes of vertebrate photoreceptors: Rods, which respond best at dim levels of illumination, and cones, which respond best in broad daylight. The cellular and molecular mechanisms of vigabatrin-induced retinal toxicity are ill-defined. Development of rodent models has only been recently initiated. Vigabatrin treatment of mice generates rapid disorganization of the photoreceptor nuclear layer, and light exposure significantly enhances drug toxicity. We hypothesize that the light-activated phosphodiesterase (PDE) that normally functions in the vision cascade mediates vigabatrin's toxicity to rod and cone photoreceptors.

To further understand the role of PDE in mediating vigabatrin's retinal toxicity, we will test the effect of vigabatrin on retinal function and histology in unique lines of mutant mice that have been engineered to exhibit diminished phototransduction responses. These mice carry mutations in phototransduction genes (Pde6gW70A and Gnat2cpfl3, respectively), and if vigabatrin toxicity does indeed require rod or cone phototransduction, the mutant mice should be protected from the vigabatrin treatment.

Vigabatrin-induced loss of visual field is asymptomatic, and hence this devastating problem can be overlooked, especially in children with TSC37. The most successful ophthalmologic methods for detecting vigabatrin toxicity in TSC children are visual field and full-field electroretinogram (ERG) screening. Formal visual field testing or ERG is not practical in children with TSC. However, we have preliminary evidences that non-invasive Optical Coherence Tomography (OCT) imaging can detect and monitor retinal pathology in individuals with TSC.

Results from our study will better elucidate the mechanisms by which vigabatrin damages the retina, and may provide better disease detection and management in children with TSC taking vigabatrin. For instance, if the role of PDE signaling proves necessary for vigabatrin-induced retinopathy, physicians could advise patients to limit light exposure, prescribe sunglasses, and/or PDE activity inhibitor drugs (such as Viagra).