

Vigabatrin: The Problem of Monitoring for Peripheral Vision Loss in Children

“Vigabatrin (Sabril) is an irreversible inhibitor of synaptic GABA-transaminase. It thereby increases brain levels of GABA, the major inhibitory neurotransmitter. Vigabatrin has been used around the world to treat epilepsy since the early 1990’s and has recently been approved for use in the United States.

Vigabatrin is approved for the management of refractory, complex partial seizures in adults who have failed a number of other anti-epileptic drugs. However, in the pediatric population, Vigabatrin is one of only two approved first line treatments for infantile spasms (IS, West syndrome). Although adrenocorticotrophic hormone (ACTH) is also a first line therapy for IS, it has the potential for considerably greater adverse side effects.

In 1997 several cases of peripheral visual field loss associated with Vigabatrin were described¹. Since that time, it has become apparent that Vigabatrin may cause permanent, concentric peripheral visual field loss, thought to be secondary to drug-induced injury to both the retinal photoreceptors and the retinal ganglion cells and their axons. Most studies conclude that there is a correlation between the peripheral visual field defects and cumulative dose^{2,3}. The majority of children and adults with field defects have taken the drug for more than a year. However, the degree to which signs of retinal toxicity signify irreversible retinal damage or early signs of a progressive toxicity that can be arrested has not been established.

This has led to the recommendations to control the dose to 3 gm per day in adults, or 50-100 mg per kg per day in children as a maintenance dose. It should be withdrawn if it fails to provide desired anticonvulsant effects. Ocular side effects of the drug should be monitored, whenever possible.

As recommended by the FDA, patients should have complete eye examinations and visual field testing (the most sensitive test is automated static perimetry) prior to the initiation of the drug. Follow up examinations to monitor for visual field defects and other ocular side effects should occur every 3 months. Although some children may be able to perform perimetric testing and undergo careful fundus examinations, unfortunately, the vast majority of children who receive Vigabatrin are very young, nonverbal, and unable to cooperate with the tests that are most the most sensitive for detecting the earliest changes caused by Vigabatrin. The purpose of this communication is to comment on this problem of monitoring of visual system side effects of Vigabatrin in children. Without visual

field testing the ophthalmologist caring for such children may have to rely on alternative methods to evaluate for Vigabatrin toxicity.

1. Serial fundus examinations: Although the fundus may remain entirely normal in appearance even when alterations to visual field occur from Vigabatrin toxicity, retinal examinations may offer the best method for detection of Vigabatrin toxicity in nonverbal patients. Changes to the optic nerve may occur, as may thinning of the nasal retinal nerve fiber layer, termed "inverse optic atrophy."^{4, 5, 6} Coincident changes can include pigment epithelial changes in the macula, and a membranous appearance to the retina.

2. Serial Automated Static Perimetric Examinations: The degree of sensitivity required by this test for the detection of visual field changes makes it practical and reliable only in high-functioning children, probably those at least 9 years of age who are able to cooperate for testing. Although visual field exams can be performed on younger children, they are not sensitive enough to detect subtle field changes.

3. Ocular Coherence Tomography: This test, too, requires cooperation on the part of the young patient and is unlikely to be reliable in nonverbal and young children.

4. Visual Evoked Potentials: Initial enthusiasm for various types of evoked potentials has been tempered by the realization that in individual subjects, the tests are simply too unreliable to guide decision-making with regards to Vigabatrin maintenance.

5. Electroretinograms: The ERG can be monitored in serial fashion to detect changes in the retina brought about by Vigabatrin therapy⁷; however, problems are associated with this approach. The first of these is that the ERG amplitudes and latencies undergo developmental changes. The paucity of normative data on young children for comparison may interfere with analysis of the waveform. Second, testing in young children generally requires sedation or general anesthesia, which also may alter the waveform. In addition, ERG testing every 3-6 months in young children is inconvenient, costly and potentially dangerous. Based on the current literature, serial ERGs as a means of detecting Vigabatrin toxicity cannot be recommended.

Conclusion: Under the best of circumstances, the ophthalmologist and neurologist would be able to follow a child on Vigabatrin for early visual field changes. This is not possible in nonverbal, uncooperative or very young patients. The physicians responsible for monitoring children on Vigabatrin can offer serial fundus examinations to detect retinal changes. Given the inability to detect early changes to the visual system in many children on Vigabatrin, the ophthalmologist, neurologist, and the child's family must weigh the gains made

with Vigabatrin therapy against the possible changes in vision which could result. There may be situations, such as in children with cortical visual impairment, where a decision is made to continue treatment for seizure control even after ocular effects are documented. Children should be periodically evaluated to ensure that Vigabatrin therapy remains effective, and continues to be a therapy required to suppress seizures, when no other treatment will work. It is hoped that future research will offer treating physicians better approaches to the diagnosis of visual field changes in this group of children.

¹ Eke T, Talbot JF, Lawden MC. (1997) Severe persistent visual field constriction associated with vigabatrin. *BMJ* **314**: 180-1.

² Malmgren K, Ben-Menachem E, Frisen L. (2001) Vigabatrin visual toxicity: evolution and dose dependence. *Epilepsia* **42**: 609-15.

³ Hardus P, Verduin WM, Engelsman M, Edelbroek PM, Segers JP, Berendschot TT, Stilma JS. (2001) Visual field loss associated with vigabatrin: quantification and relation to dosage. *Epilepsia* **42**: 262-7.

⁴ Frisen L, Malmgren K. (2003) Characterization of vigabatrin-associated optic atrophy. *Acta Ophthalmol Scand* **81**: 466-73.

⁵ Wild JM, Robson CR, Jones AL, Cunliffe IA, Smith PE. (2006) Detecting vigabatrin toxicity by imaging of the retinal nerve fiber layer. *Invest Ophthalmol Vis Sci* **47**: 917-24.

⁶ Buncic JR, Westall CA, Panton CM, Munn JR, LD McKeen LD, Logan WJ. (2004) *Ophthalmology* 101: 576-580.

⁷ Krauss GL, Johnson MA, Miller NR. (1998) Vigabatrin-associated retinal cone system dysfunction: electroretinogram and ophthalmologic findings. *Neurology* **50**: 614-8.

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