

Vigabatrin Retinal Toxicity First Detected with Electroretinographic Changes: A Case Report

Dianne Barrett¹, Jin Yang², Tharikarn Sujirakul², and Stephen H. Tsang^{2,4*}

¹College of Physicians & Surgeons, Columbia University, New York, NY 10032, USA

²Edward S. Harkness Eye Institute, Columbia University, New York, NY 10032, USA

³Bernard & Shirlee Brown Glaucoma Laboratory, Departments of Ophthalmology, Pathology & Cell Biology, Columbia University, New York, NY 10032, USA

⁴New York-Presbyterian Hospital/Columbia University Medical Center, New York, NY 10032, USA

*Corresponding author: Stephen H. Tsang, Edward S. Harkness Eye Institute, New York-Presbyterian/Columbia University Medical Center, 160 Fort Washington Ave. Research Annex, Room 513, New York, NY 10032, USA, Tel: +212 3421189; Fax: +212 3054987; E-mail: sht2@columbia.edu, dab2167@columbia.edu

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Abstract

Vigabatrin is an effective antiepileptic drug (AED) typically used in the treatment of refractory partial seizures and infantile spasms. Its use, however, is limited due to the concern of retinal toxicity and subsequent visual field defects. Herewith we describe a case of vigabatrin toxicity that illustrates electroretinographic (ERG) changes occur before imaging and visual field deterioration. Decrease in maximal ERG b: a ratio was observed before thinning of the retinal nerve fiber layer (RNFL) on optical coherence tomography (OCT).

Keywords: Vigabatrin; Retinal toxicity

Introduction

Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the CNS. Vigabatrin (VGB) produces its antiepileptic effects by irreversibly inhibiting GABA transaminase, an enzyme responsible for GABA degradation. This inhibition leads to decreased breakdown of endogenous GABA, higher GABA levels and decreased neuronal activity [1]. Clinically, VGB is often used in combination with other antiepileptic drugs as third or fourth line efforts to address pharmacoresistant complex partial seizures and first line for infantile spasms. As to its effectiveness, European, Canadian and American groups have found significant responder rates i.e. seizure reduction and even elimination typically within two weeks of starting the medication [2]. In 1997, VGB-induced retinal damage was first reported in three individuals with severe peripheral visual field defect (VFD). Today, the prevalence of VGB-induced peripheral VFD is estimated at 25-50% in adults, 15% in children and 15-31% in infants. Typically, patients with VGB-induced retinal toxicity are asymptomatic, though there have been reports of oscillopsia, blurred vision, tunnel vision and difficulty in navigation [3].

Moreover, most patients with VGB-induced retinal toxicity have normal visual acuity and color vision [4]. Abnormal fundoscopic findings include: optic nerve pallor, retinal wrinkling, peripheral retinal arteriolar narrowing and subtle macular reflex changes [5]. Furthermore, two studies using OCT to evaluate vigabatrin retinal toxicity found evidence of retinal nerve fiber layer (RNFL) thinning with associated visual field loss [6]. On examination of the visual field, patients usually present with bilateral nasal wedge defects that can progress to concentric, bilateral field loss. The degree of visual field loss is typically symmetric in both eyes [2]. Electrophysiological testing

in patients with VGB-induced retinal toxicity demonstrate abnormalities in electroretinogram (ERG) and electrooculargraphy (EOG). On ERG, the most consistent presentation is a reduction in cone b-wave amplitude. Additional findings can include, rod b-wave reduction, implicit time delay and reduced oscillatory potential [7,8]. On EOG, patients have a reduced Arden Index which can improve to normal after cessation of the medication. Notably, the majority of patients have persistent visual field defects despite improvement of ERG and EOG after discontinuation of the drug [9]. Most screening guidelines on VGB retinal toxicity rely heavily on monitoring visual fields as evidence of toxicity [2]. However, in this case we report ERG abnormalities occurring years in advance of imaging and visual field defects.

Case Report

The patient is a 46 year old woman with symptomatic generalized epilepsy with periventricular gray matter heterotopias. She began having seizures at 14 years old. They have been very difficult to control, thus managed with a variety of antiepileptic regimes. She was referred by her neurologist to establish an ophthalmologic baseline prior to starting vigabatrin therapy. The patient denied visual complaints. Visual acuity was 20/20 OU, tonometry was normal, extraocular movements were intact and visual fields full to confrontation. Anterior and posterior segment exams, ERG, Humphrey 24-2 visual field were grossly normal. She was started on 2,000mg of vigabatrin twice a day for a total dose of 4,000 mg daily. She returned two months later; exam and testing were all within normal limits. However, on her second follow up visit, 5 months after starting vigabatrin therapy, the ERG was notable for decreased b:a ratio, but OCT and visual fields were unremarkable (Figure 1, 2 and 3). She had no visual complaints at this time.

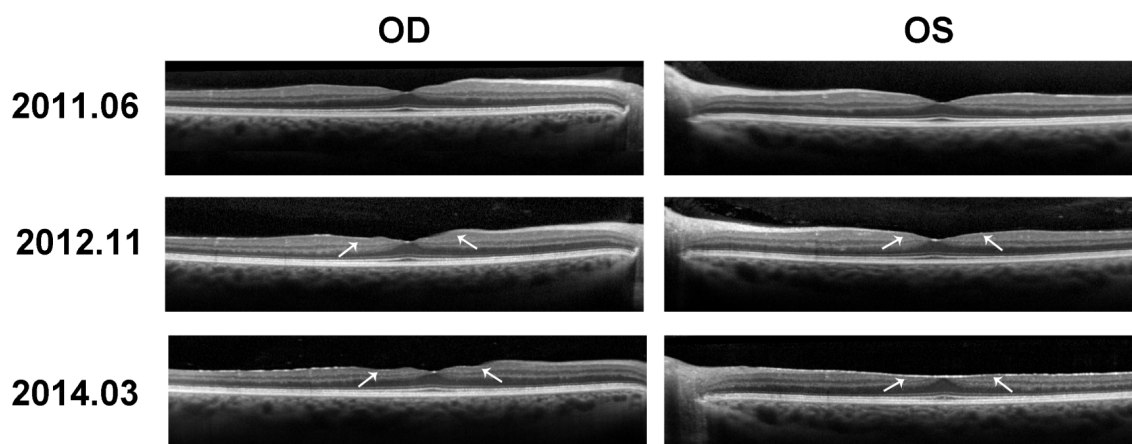


Figure 1: Optical Coherence Tomography (OCT). Images are labeled according to the date taken; each date corresponds to one set of left and right eye images. 2011.06 and 2012.11 depict normal retinal layers throughout. The left and right eye images taken 2014.03 are notable for left eye greater than right eye thinning of the retinal nerve fiber layer, ganglion cell layer, inner plexiform and inner nuclear layers with loss of the foveal pit in the left eye.

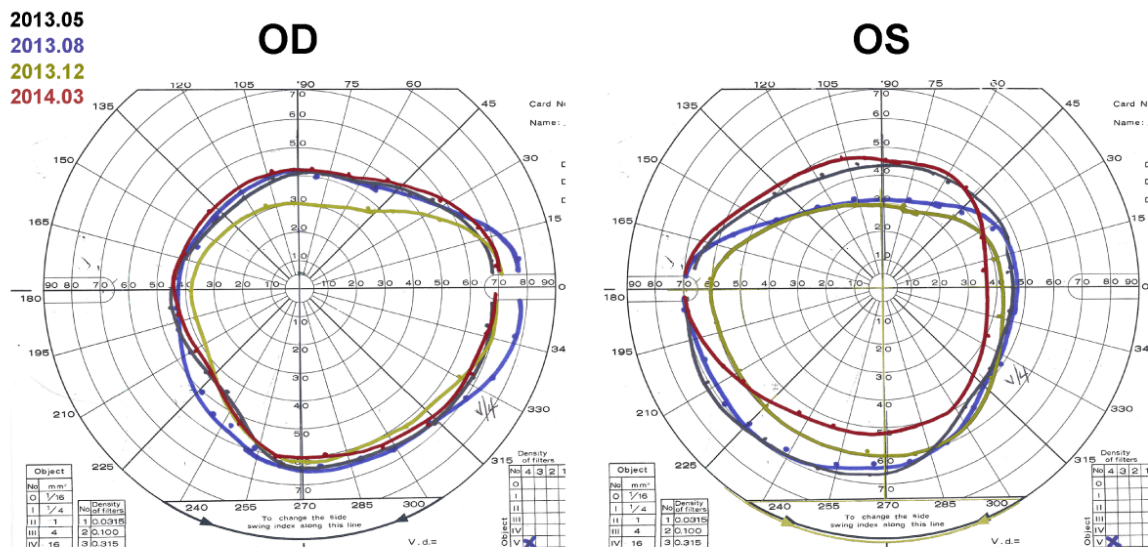


Figure 2: Goldmann perimetry field. Images show constricted visual fields. Notably, the field dated 2014.03, is moderately improved from the visual field taken four months earlier - 2013.12.

Due to the abnormal findings on ERG the dose was halved to 2,000 mg per day. On the next follow up visit 3 months later, ERG findings persisted, however visual field and OCT were again within normal limits. The dose was again halved, now to 1,000 mg daily. Eleven

months after starting VGB, the Humphrey 24-2 visual field was notable for mild peripheral superior field defects in both eyes. The decreased maximal b:a ratio first seen 6 months ago on ERG persisted (Figure 3).

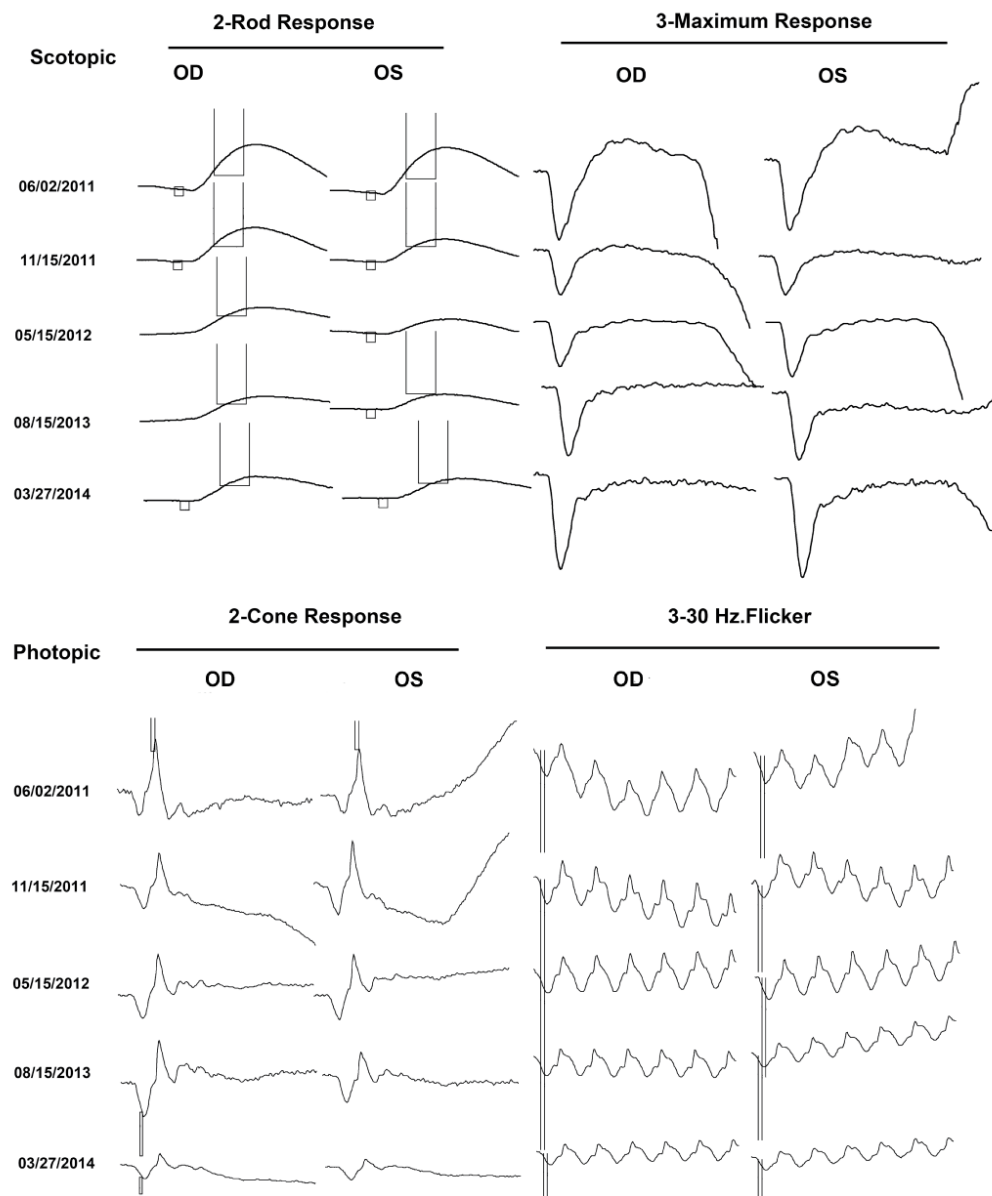


Figure 3: Electroretinogram (ERG) of both eyes. Scotopic 2-Rod Response showing bilateral decrease, though left greater than right, in wave amplitude. 3- maximum response showing decrease in b: a wave ratio. Photophopic 2-cone response and 3-30Hz flicker showing bilateral, but again, left greater than right decrease in wave amplitude.

At this time we suggested to stop the VGB or lower the dose. However, in the setting of decreased doses over the prior months the patient suffered more seizures, thus the dose was returned to 2,000 mg twice a day. She was maintained on this dose for the next 20 months. Over this time, Goldman visual fields (GVF) showed moderate, but stable constriction-temporal fields ~70 degrees OU (Figure 2). OCT was within normal limits (Figure 1). ERG consistently showed a decreased b:a ratio and decreased 30Hz flicker amplitude (Figure 3). Thirty three months after starting VGB therapy the patient presented

for routine follow up with complaints of significant decrease in vision. Visual acuity was 20/25 OD and 20/150 OS, there was an afferent pupillary defect in the left eye, OCT and RNFL mapping showed marked thinning of the nerve fiber layer (Figure 3, 2014.03; Figure 4), but the GVF showed moderate improvement from previous studies (Figure 2, 2014.03). At this time, we conferred with her epilepsy specialist and decided to stop VGB therapy. At the preparation of this report her vision had not improved.

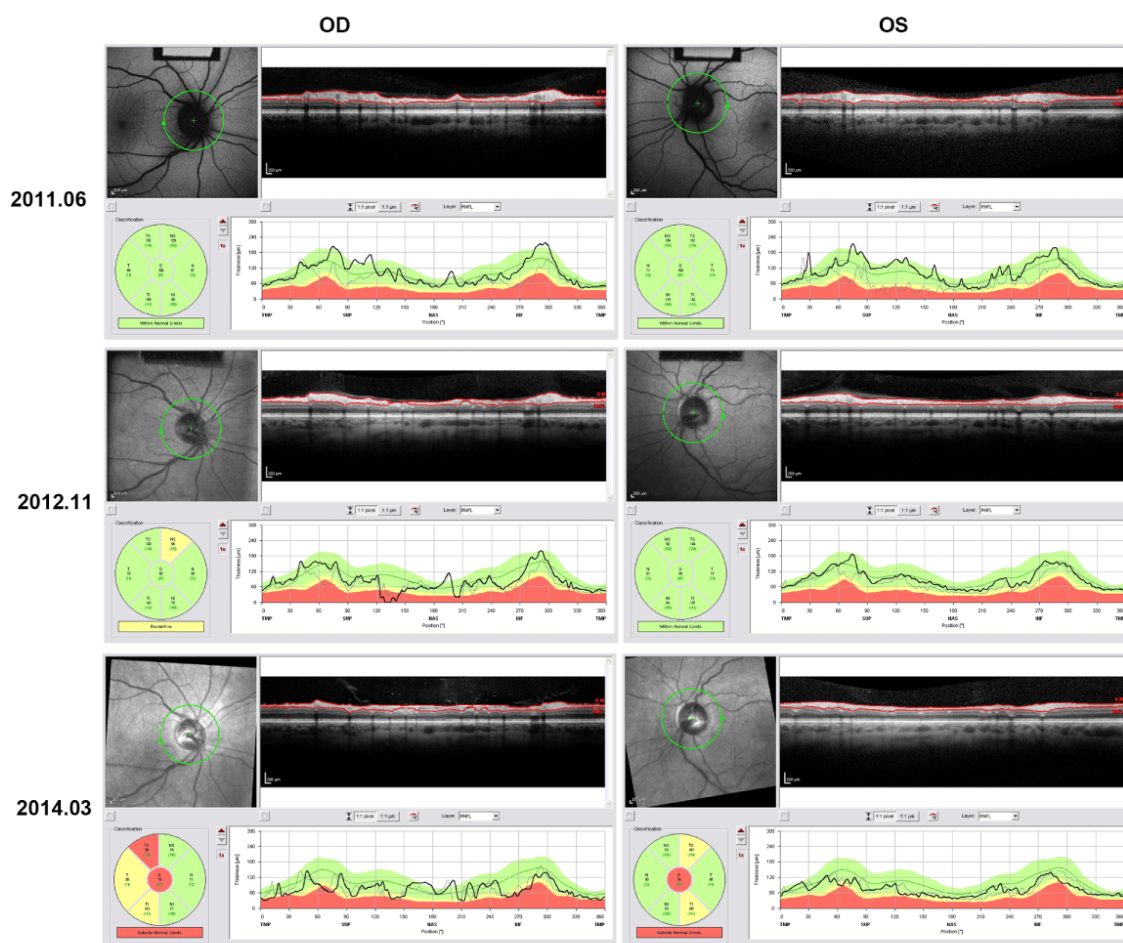


Figure 4: Retinal Nerve Fiber Layer (RNFL) Thickness Map. RNFL map showing bilateral decrease in RNFL thickness over time with left RNFL loss greater than right. Green corresponds to normal RNFL thickness, yellow borderline, and red below normal and borderline thickness. Anatomic orientation - T: temporal, S: superior, I: inferior, N: nasal.

Discussion

VGB induced retinal toxicity is a well-known possible side effect of VGB therapy. Despite awareness of its occurrence we have yet to fully elucidate the pathophysiological mechanism. Interestingly, most evidence indicates that the retinal damage associated with VGB is due to the therapeutic effects of the drug specific to its accumulation in the retina [1,6]. Increasing retinal GABA levels leads to unwarranted and prolonged retinal cellular membrane depolarization, subsequent influx of Cl^- , Na^+ and water leading to homeostatic imbalance and cellular demise [10]. This excitotoxicity does not appear to be a class effect. According to a study by Sills and colleagues tiagabine-a GABA reuptake inhibitor-does not seem to cause the visual field or ERG abnormalities seen with VGB. This may be due wholly or in part to the fact that tiagabine does not accumulate or increase GABA concentrations in the retina [11].

Since researchers and clinicians became aware of VGB retinal toxicity questions of how best to monitor for this characteristically irreversible side effect arose. Importantly, the method employed should be able to quickly and efficiently detect toxicity before

symptomatic vision loss. Peripheral visual field defect was the first and continues to be the most reported ocular presentation associated with VGB retinal toxicity [2]. Thus, VGB retinal toxicity guidelines tend to rely heavily on visual field testing to screen for VGB retinal toxicity in children and adults [2,3]. In this case the patient's visual field was relatively stable over the course of her treatment with VGB (Figure 2). In fact, when the patient presented with an acute decrease in central visual acuity the visual field at that time was similar to previous fields (Figure 2, 2014.03). However, the patient's ERG had consistently showed decreased b:a wave ratios, and decreased 30Hz flicker amplitudes since 5 months after starting VGB (Figure 3).

It has been suggested that OCT be used to screen for VGB induced retinal toxicity because this test can show thinning of the RNFL which is associated with visual field loss [12]. Notably, here, the patient's OCT was normal until the acute presentation of decreased visual acuity (Figure 1, 2014.03). Therefore, in cases such as this OCT has limited application as a screening tool because it alerts the clinician to an abnormality after the patient has become significantly symptomatic. Also, as Figure 2 demonstrates in cases such as this, visual field testing has limited application. Though the visual fields did

show some constriction it was mild and unreliable as the patient had somewhat improved visual fields when she presented with an acute deterioration in visual acuity (Figure 2). Moreover, this case is unique in that the patient's visual symptoms were much more pronounced in the left eye when most cases report bilateral involvement. Because we are in the infancy of understanding VGB induced retinal toxicity the data is limited on how to limit toxicity in patients who cannot stop the medication. Some groups using animal studies have suggested that supplementation of an amino acid- taurine may help to prevent or treat VGB retinal toxicity given that taurine plays a role in retinal excitability and free radical generation [6]. However, the authors concede more studies are necessary before a widespread recommendation can be supported. Moreover, other groups have demonstrated the role of phototransduction in enhancing vigabatrin toxicity. In this study, mice with altered phototransduction pathways- thus a decreased ability to perceive light- have decreased incidence of VGB retinal toxicity [1]. This observation suggests decreasing light exposure i.e by wearing sunglasses or avoiding excess light might help treat and/or prevent VGB retinal toxicity.

In sum, this report details a case of VGB retinal toxicity which was first identified via ERG abnormalities. It provides a snapshot of the complex world of retinal physiology and the drugs that can affect the retina. This case also affirms that monitoring for VGB retinal toxicity should not be a one-size-fits-all approach. Here, as a single modality ERG demonstrated retinal dysfunction early-before OCT and perimetry- and before the patient was visually symptomatic. This testifies to the usefulness of this exam to screen for and monitor VGB induced retinal toxicity. Ideally, we recommend cessation of VGB when ERG changes occur. However, we understand that may not be easily done or possible for some patients whose seizures return or worsen- as it was in this case- with decreased doses or cessation of VGB. Moreover, in patients with visual field or visual acuity abnormalities we agree with current guidelines that an evaluation of the risks and benefits of decreased dose or cessation of VGB must be weighed against the effect of the vision changes on the patient's functionality. More work is necessary to better carve out the exact mechanism of VGB retinal toxicity, how to best monitor for retinal damage before symptomatic visual loss and how to treat and even prevent this side effect.

Acknowledgment

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