Retinal Function Abnormalities in Patients Treated With Vigabatrin

Eyal Banin, MD, PhD; Ruth S. Shalev, MD; Alexey Obolensky, MD, PhD; Ruhama Neis; Itay Chowers, MD; Varda Gross-Tsur, MD

Objective: To evaluate central and peripheral retinal function in patients treated with vigabatrin, an antiepileptic drug associated with peripheral visual field constriction (VFC).

Methods: Six patients with epilepsy treated with vigabatrin as add-on therapy for at least 3 years were included in this observational case series. All patients underwent a clinical ophthalmologic examination, color vision testing, standard perimetry, and full-field and focal foveal cone electroretinography. Four patients, 3 of whom had VFC, completed specialized computerized static light- and dark-adapted perimetry.

Results: In 9 of 11 eyes tested, foveal cone electroretinographic amplitudes were at or below the lower limit of normal. Dark-adapted perimetry demonstrated abnormal rod-derived visual fields in the 3 patients with vigabatrin-attributed VFC, whereas rod-derived thresholds were within normal limits throughout the visual field in the patient who did not have VFC.

Conclusions: Our results suggest that vigabatrin not only impairs peripheral cone-derived function as manifested by VFC but also affects foveal cone electroretinographic amplitudes and rod-derived visual fields. The clinical dilemma regarding the use of vigabatrin therapy is further complicated since central as well as peripheral visual function seems to be adversely affected.

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Vigabatrin (the γ-vinyl analogue of γ-aminobutyric acid [GABA]) is a selective, enzyme-activated, irreversible GABA amino-transferase inhibitor.1 It is a custom-made antiepileptic drug (AED) found to be particularly useful in the management of drug-resistant partial seizures and infantile spasms, especially those secondary to tuberous sclerosis.2-4 The antiepileptic effect is presumably mediated by elevation of GABA levels of the brain caused by inhibition of GABA metabolism.3

Initially, only relatively minor adverse effects were attributed to vigabatrin use.5 Over the last decade, the marked efficacy of this medication and its low toxic effects prompted widespread use in Europe. Recently, visual field abnormalities were reported in adults and children treated with this AED. In most documented cases, the visual field defect seems to be a specific, bilateral, and symmetrical peripheral constriction.6-7 The fact that most patients are asymptomatic may have contributed to the late recognition of these visual field defects that apparently occur in more than 30% of the patients.10-13

Previous reports emphasized that vigabatrin therapy induced peripheral cone-derived visual field constriction (VFC). However, intimations of central cone dysfunction were reported by Johnson et al.,14 Nousiainen et al.,15 and Hilton et al.,16 who noted that visual acuity, color vision, contrast sensitivity, and central short wavelength automated perimetry results can also be affected. In addition, recent studies reported abnormalities not only in cone-derived but also in rod-derived electroretinographic (ERG) responses, namely, rod b waves, scotopic oscillatory potentials, or both.11,17,21 The objectives of our study were to electrophysiologically evaluate central cone function in patients with epilepsy who were treated with vigabatrin and to examine psychophysically whether impairment of rod-derived visual fields accompanies the cone-derived VFC in these patients.

METHODS

Six patients with epilepsy treated with vigabatrin as add-on therapy for at least 3 years were included in this observational case series. They were carefully chosen from among the more than 30 patients who had epilepsy treated with vigabatrin. We selected these patients for their
light (to suppress stray activation) was directed on the fovea stimulus subtending 4° on the retina within a 12° anulus of bright a commercial computerized system (MaculoScope Spectrum; performed using Burian-Allen contact lens electrodes (Hanand signal averaging was used. Focal foveal cone ERGs were acquired. All ERG responses were filtered at 0.3 to 500 Hz was acquired—a rod response to a dim blue flash (Wratten filter Gaithersburg, Md). In the dark-adapted state, 2 responses were acquired in a control group of 6 consecutive epileptic patients with disease of comparable severity (age range, 14-27 years) who were being treated with multiple AEDs but have not received vigabatrin.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Seizure Type</th>
<th>Additional Antiepileptic Medications</th>
<th>Daily Dosage, g/d (mg/kg)</th>
<th>Cumulative Dose, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/18</td>
<td>CP S/P surgery</td>
<td>Carbamazepine and phenytoin</td>
<td>3</td>
<td>5 (30)</td>
</tr>
<tr>
<td>2/M/5</td>
<td>CP</td>
<td>Carbamazepine</td>
<td>4.5</td>
<td>2.5 (35)</td>
</tr>
<tr>
<td>3/M/14</td>
<td>CP</td>
<td>Carbamazepine</td>
<td>5</td>
<td>2.5 (45)</td>
</tr>
<tr>
<td>4/M/17</td>
<td>Multiple types</td>
<td>Lamotrigine and felbamate</td>
<td>6</td>
<td>3 (65)</td>
</tr>
<tr>
<td>5/M/45</td>
<td>S/P surgery</td>
<td>Valproic acid</td>
<td>6</td>
<td>2 (25)</td>
</tr>
<tr>
<td>6/M/33</td>
<td>S/P surgery</td>
<td>Carbamazepine</td>
<td>6.5</td>
<td>1.5 (25)</td>
</tr>
</tbody>
</table>

Abbreviations: CP, complex partial; S/P, status post.
*Dosage was occasionally adjusted during treatment. Numbers represent approximate average dose over treatment period.

All patients underwent focal foveal cone ERG testing, using a 42-Hz flickering stimulus. The results of 8 test sets (averaging 2500 stimuli per set) in the right eye of patient 2 are shown in Figure 1A. Amplitudes of the averaged responses were borderline low while implicit times were within normal limits. Goldmann perimetry in this eye shows the typical constriction associated with the toxic effect of vigabatrin therapy (Figure 1B). In 9 of 11 eyes tested, foveal cone ERG amplitudes were similar at or below the lower limit of normal (Figure 1C; patient 4 allowed only 1 eye to be tested). Foveal cone implicit times were normal in all eyes. Amplitudes of the focal foveal cone ERG responses were within the normal range in 10 of 12 eyes tested in a control group of 6 epileptic patients with disease of similar severity who were not being treated with vigabatrin. In 1 eye each of 2 patients, amplitudes were reduced (0.14 µV and 0.09 µV; lower limit of normal, 0.18 µV).

On full-field ERG, which measures the mass response across the entire retina, cone 30-Hz flicker amplitudes were normal in patient 1, slightly below the lower limit of normal in patient 3, and markedly reduced in patients 4 through 6. Implicit times were borderline in patient 4 and delayed in patients 5 and 6 (Table 2). Light-adapted (cone-derived) visual fields showed characteristic vigabatrin-associated peripheral constriction in patients 2, 4, 5, and 6 (patient 5 also had post-

willingness to cooperate in visual function testing and for their ability to maintain stable fixation and concentration, which are required for reliable visual field and focal ERG testing. The following data were collected: patient demographics, seizure type, other AEDs, duration of vigabatrin therapy, and dosage (Table 1). Patients and parents, where appropriate, gave their informed consent to all procedures.

A routine ophthalmologic examination including assessment of visual acuity, ocular motility, pupillary reaction, and dilated fundus as well as an examination using a biomicroscopy slitlamp was performed in all patients. Subsequently, kinetic and/or static perimetry, color vision testing, full-field, and focal foveal cone ERGs were performed according to cognitive function of the patients and their degree of cooperation.

Goldmann kinetic perimetry was performed using targets V-4-e, III-4-e and, in some cases, 1-4-e on a 10-candela (cd/m²) white background. Standard static perimetry was performed using a visual field analyzer (Humphrey Field Analyzer; Allergan-Humphrey, San Leandro, Calif) using the 120-point screening test or programs 30-2 (or 24-2) and 30/60-2 when subject cooperation permitted. In 4 patients, specialized light- and dark-adapted static threshold perimetry was performed using a modified automated perimeter according to methods previously published by Jacobson et al. Briefly, 71 loci (12° grid) were tested across the visual fields to identify threshold intensities of 300-nm (blue) and 630-nm (red) stimuli that, in the dark-adapted state, can be used to differentiate between rod- or cone-mediated detection. In the light-adapted state, 600-nm (orange) stimuli on a 10-cd/m² white background were used. Rod-derived (at 500 nm) and cone-derived (at 650 nm) stimuli that, in the dark-adapted state, can be used to differentiate between rod- or cone-mediated detection.

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Full-field ERGs were recorded using corneal electrodes and a computerized system (Cyberscan model 4000; Microshev, Efrat, Israel; or UTAS 3000; LKC Technologies Inc, Gaithersburg, Md). In the dark-adapted state, 2 responses were acquired—a rod response to a dim blue flash (Wratten filter No. 47b) and a mixed cone and rod response to a white flash (2.35 cd × s/m²). In the light-adapted state, a background light of 21.3 cd/m² was used to suppress rods; the cone response to flashes of white light (9.4 cd × s/m²) was measured at 1 and 30 Hz was acquired. All ERG responses were filtered at 0.3 to 500 Hz and signal averaging was used. Focal foveal cone ERGs were performed using Burian-Allen contact lens electrodes (Hansen Ophthalmic Development Laboratory, Iowa City, Iowa) and a commercial computerized system (MaculoScope Spectrum; Dornan Instruments Inc, Littleton, Mass). A 42-Hz flickering stimulus subtending 4° on the retina within a 12° anulus of bright light (to suppress stray activation) was directed on the fovea or parafoveally using a Maxwellian view handheld system. Because of the difficulty of positioning the stimulating beam precisely and steadily on the fovea during recording, accurate and reliable testing with the focal ERG system is a challenging task and is highly dependent on the operator and subject. All tests in this study were performed by 1 of 2 operators (E.B. or A.O.), who had the experience of performing such testing in more than 540 patients (>1000 eyes) during the last 5 years. Recording was immediately stopped if fixation on the fovea was unstable and was resumed only when the beam was again well aimed. In addition, at least 4 sets of responses (each averaging 2500 waveforms) were collected in each eye. “Clustering” of the results of the different sets (ie, repeatability) helped to assess reliability of the recording. Focal foveal cone ERG testing was also performed in a control group of 6 consecutive epileptic patients with disease of comparable severity (age range, 14-27 years) who were being treated with multiple AEDs but have not received vigabatrin.

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surgical right superior quadrianeopsia). Patient 1 had left superior quadrianeopsia (following surgery) but no constriction in other quadrants. Patient 3 had preserved visual fields. To assess peripheral rod-derived visual fields, dark-adapted perimetry was performed in 4 patients in addition to light-adapted perimetry. Patients 4 through 6 had cone- and rod-derived thresholds that were significantly elevated, ie, more than 2 SDs higher than the mean, in many peripheral loci (testing results of patients 4 and 5 are shown in Figure 2). Note that full-field cone flicker and rod b-wave ERG amplitudes were borderline or low while implicit times were within the normal range. B, Goldmann kinetic visual fields in the same right eye show visual field constriction (VFC) in the pattern typical for the toxic effects of vigabatrin therapy. C, The histograms show average foveal cone ERG amplitudes in 6 patients treated with vigabatrin for at least 3 years. Five of the patients, 4 of them with VFC, had amplitudes at or below the lower limit of normal (indicated by the dotted line [0.18 µV]).

Visual field constriction, which occurs in more than 30% of the treated patients, has recently emerged as a significant toxic adverse effect of vigabatrin therapy.10,12,13 The pathologic features of VFC have been attributed mainly to the loss of peripheral cone–mediated vision,11,23,24 but recent findings have intimated that there may be a generalized decrease of cone sensitivity across the central and peripheral visual fields.14 Our findings confirm these initial observations. Using focal foveal cone ERG, we found that central (foveal) cone function was impaired. In ad-
dation, rod-derived visual fields, as tested by dark- 
adapted perimetry, were constricted in patients with cone-
mediated VFC. This may be the psychophysical correlate 
to reduced scotopic ERG b-wave amplitudes and abnor-
mal scotopic oscillatory potentials reported in some of 
the patients treated with vigabatrin.11,17-21 While all of our 
patients were receiving additional AEDs, the results of 
Coupland et al17 support the notion that these signs of 
toxic reactions are vigabatrin related.

Foveal cone dysfunction is a particularly worrisome 
finding since the consensus has been that central vision, 
as measured by visual acuity, perimetry, and color vision, 
was preserved in patients treated with vigabatrin.9,11 This 
was reassuring information for patients, parents, and physi-
cians who were called on to decide between seizure 
control and the risk of VFC. However, preliminary psycho-
physical evidence that visual acuity, color vision, central 
short wavelength automated perimetry, and contrast sen-
sitivity may also be impaired has recently been published.10,14-16 There are only a few electrophysiological stud-
ies assessing foveal function (all using the multifocal ERG 
technique) with conflicting results: in 3 studies, the mul-
tifocal ERG revealed changes in the responses recorded from 
the periphery while central responses were considered nor-
mal.24-26 Only 1 study showed diffuse perturbation of cone 
function in 3 patients.14 Multifocal ERGs were also per-
fomed in 8 additional patients with known vigabatrin-
attributed VFC.27 The issue of central involvement was not 
directly commented on in this fourth study. In some cases 
there was good concordance between the visual field de-
fects and the multifocal ERG abnormalities, but in others 
the ERG abnormality was more diffuse than the visual field 
defect.

In our study we used focal foveal cone ERG, a dif-
ferent technique that allows assessment of foveal cone-
derived electrophysiological function under direct visu-
alization. The abnormal results obtained in most patients 
in conjunction with the preliminary results of Johnson 
et al14 support the contention that vigabatrin therapy does 
not spare central cone function. Based on this finding, 
we would like to propose that generalized retinal dys-
function can be induced by vigabatrin therapy. The elec-
trophysiological abnormality on focal foveal cone ERGs 
could be part of the cone flicker amplitude reductions 
previously reported using full-field ERGs.10,14,24 It is pos-
sible that the relative preservation of visual acuity and 
color vision is a function of the high density of cones in 
the macula that affords a “sparing effect” despite the elec-
trophysiological abnormalities. However, compromise of 
central vision may ultimately occur with prolonged use 
or high accumulative doses of vigabatrin.

Rod-derived visual field impairment was not previ-
ously reported in patients treated with vigabatrin. The toxic 
effect of this medication is, thus, not restricted to the cone-
derived system. This finding is in accord with the reports 
of reduced scotopic ERG b-wave amplitudes11,17,21 also ob-
served in 3 of our patients. However, a longitudinal study 
in children treated with vigabatrin did not find a substi-
tial change in rod-derived ERG responses over an 18-
month follow-up period.28 The site and mechanism of the 
toxic effects of vigabatrin therapy are unknown. Multiple 
retinal cells are GABAergic, including several subtypes of 
cone and rod bipolar cells as well as many subtypes of ama-
crine cells.29,30 Animal studies demonstrated retinal outer 
layer nuclear layer destruction with a peripheral disposi-
tion.31 However, most studies tend to attribute the ERG changes 
caused by vigabatrin to effects on the inner retina. Ama-
crine cell involvement has been implicated.21,23,32 as well as 
as a possible toxic effect on Muller cells.9,11,17 The elevat-
ed thresholds on psychophysical testing in the present study 
could point to impairment of bipolar cell function.33 In 
addition, a postmortem study suggests that vigabatrin may 
be toxic to ganglion cells, resulting in loss of nerve fibers 
in the optic nerves, chiasm, and tracts.34 The long-term outcome of vigabatrin-induced cen-
tral cone dysfunction is as yet unknown. Vigabatrin-
influenced VFC persists, at least for the short-term, follow-
ing discontinuation of the medication in most cases.29,35 On 
the other hand, there is some evidence that in 
patients with minimal VFC, visual acuity and color 
vision deficits may be reversible with improvement in 
some of the electrophysiological alterations (such as

<table>
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<th>Table 2. Visual Function Testing</th>
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<tr>
<td>Patient</td>
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<tr>
<td>---------</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>1</td>
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<td>6</td>
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Abbreviations: Abn, abnormal; D-15, Farnsworth D-15 panel test; Deut, deuteranopia; FFERG, full-field electroretinography; Ish, Ishihara 38-plate color vision test; IT, implicit time; N, normal; ND, not done; VFC, visual field constriction.
the electro-oculogram Arden ratio and ERG oscillatory potentials).\textsuperscript{11,14,23,25,32} We have not yet had the opportu-
nity to examine foveal cone ERGs serially in such cases, which would help assess the significance of the electro-
physiological finding. The small number of patients thus far tested also precludes drawing conclusions regarding possible correlation between degree of VFC, visual acu-
ity, and foveal cone ERG amplitudes. However, in the complex dilemma of whether to use vigabatrin therapy in patients for whom this is the only effective AED, the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Cone-derived (light-adapted) and rod-derived (dark-adapted) static perimetry results. Left eye of a healthy subject (top) shows mild elevations of threshold sensitivity in only 1 or 2 loci. The physiological blind spot is represented by a black square 12° temporal to fixation. A superonasal scotoma is present in the right eye visual fields of patient 1, secondary to a surgical procedure. Note the normal to mildly elevated cone- and rod-derived thresholds at most loci outside the scotoma. Both cone- and rod-derived thresholds are significantly elevated in the left eyes of patients 4 and 5. Changes are especially severe in the periphery with resulting visual field constriction (VFC). Gray-scale bars indicate degree of threshold sensitivity elevation in log units for cones and rods. N indicates nasal; T, temporal; S, superior; and I, inferior to fixation in degrees. For details see “Methods” section.}
\end{figure}

risk for eventual central visual impairment should, in our opinion, be considered.

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