Detecting Vigabatrin Toxicity by Imaging of the Retinal Nerve Fiber Layer

John M. Wild,1 Catherine R. Robson,1 Adrian L. Jones,2 Ian A. Cunliffe,3 and Philip E. M. Smith4

PURPOSE. To quantify retinal nerve fiber layer thickness (RNFLT) and macular thickness (MT) in patients exhibiting vigabatrin-attributed visual field loss (VAVFL) and to determine the efficacy of these measures as markers of the retinal damage associated with vigabatrin.

METHODS. This was a prospective cross-sectional observational study involving five groups: Group I, 13 patients exhibiting VAVFL; Group II, 8 patients exposed to vigabatrin but with normal fields; Group III, 14 patients receiving carbamazepine monotherapy; Group IV, 20 normal individuals; and Group V, 7 patients receiving sodium valproate monotherapy. At one of two visits, the right eye of each participant underwent two digital imaging modalities: ocular coherence tomography (OCT; StratusOCT; Carl Zeiss Meditec, Dublin, CA) and scanning laser ophthalmoscopy (SLO; Heidelberg Retinal Tomograph; Heidelberg Engineering GmbH, Heidelberg, Germany). At the other visit, participants underwent three-zone, age-corrected suprathreshold perimetry of the whole field and threshold perimetry of the central field. The order of the visits was randomized.

RESULTS. The group mean RNFLT in Group I was attenuated relative to that of the remaining groups (all P < 0.001). At 100% specificity, based on the 95% confidence limits derived from Group IV, OCT exhibited 100% sensitivity and SLO 77% sensitivity for an attenuated RNFLT in patients with VAVFL. All participants manifested an MT within the normal range derived from Group IV.

CONCLUSIONS. OCT of the RNFL can efficiently identify vigabatrin-induced damage and will be useful for adults and children unable to perform perimetry and when the perimetric outcome is equivocal. (Invest Ophtalmol Vis Sci. 2006;47:917–924) DOI:10.1167/iosv.05-0854

Vigabatrin, the first of the novel anti-convulsants, is used in approximately 85 countries outside the United States, as adjunctive therapy for the treatment of epilepsy of partial onset1-3 and as monotherapy for intractable spasms,4,5 particularly those secondary to tuberous sclerosis.6 Vigabatrin is a selective and irreversible inhibitor of the enzyme γ-aminobutyric acid (GABA)-transaminase, which catalyzes the inactivation of GABA, a major inhibitory neurotransmitter in the retina and cortex.7 The resultant anticonvulsant effect of vigabatrin is thought to occur from the increase in concentration of presynaptic GABA.

Vigabatrin is associated with a bilateral constriction of the visual field.8-15 The estimated prevalence of vigabatrin-attributed visual field loss ranges from 14% to 92%16 but is generally considered to be in the region of 40% to 50%.12,13,18,19 Patients with vigabatrin-attributed field loss exhibit normal visual acuity and are usually asymptomatic of the field loss unless the defect encroaches well within the central field.8,10-15 Approximately 20% of adults with epilepsy, and particularly those exposed to vigabatrin, are unable to appreciate the requirements of perimetry due to the cognitive requirements for, and the subjective nature of, the task.20 In many others, the results of perimetry can often be inconclusive and frequently require one or more confirmatory repeat examinations, even though the results of the subsequent tests can remain equivocal.

Vigabatrin-attributed field loss can exist in the presence of an apparently normal optic nerve head and retina12,23 or can be associated with optic nerve head pallor11,13,22,23 with or without a variety of accompanying subtle retinal abnormalities including surface wrinkling retinopathy9,25 peripapital retinal arteriole narrowing13,24; irregular sheen, or abnormal pigmentation, at the macula; peripheral pigmentary disturbance14,15; and thinning of either the peripapillary14 or peripheral22,25 retinal nerve fiber layer. The inconclusive and subtle nature of any coexisting optic nerve head and retinal abnormalities precludes the use of fundal examination by ophthalmoscopy as an indicator of vigabatrin-attributed field loss.

The post-mortem examination of the retina of a patient with vigabatrin-attributed field loss has indicated loss of rod and cone nuclei and extensive loss of retinal ganglion cells and their axons.24 An attenuated retinal nerve fiber layer has been described in one patient with vigabatrin-attributed visual field loss, detected by optical coherence tomography (OCT),25 and in another by confocal scanning laser ophthalmoscopy (SLO).26 However, although likely to be of particular use in the assessment of vigabatrin-induced damage, digital imaging technology of the oculan fundus has yet to be applied in a systematic manner to patients receiving antiepileptic drugs.

The overall aim of the present study, therefore, was to investigate the potential of retinal imaging to indicate vigabatrin-attributed field loss. The specific aims were to quantify, in patients with vigabatrin-attributed field loss and in patients exposed to vigabatrin but with normal fields, retinal nerve fiber layer and macular thicknesses by OCT, and the retinal nerve fiber layer thickness by SLO, thereby determining whether any of these measures could be used as a marker for vigabatrin-attributed retinal damage. The two different imaging modalities were evaluated to determine which technique, if any, possessed the better sensitivity and specificity. If structural mark-
ers could be determined, it is possible that such changes might occur before the visual field loss became established.

METHODS

The study was of a cross-sectional prospective observational design.

Cohort

The cohort comprised five groups of consecutively presenting patients and normal individuals, aged 18 years or older, who had volunteered to take part in the study after invitation by letter. Group I comprised 13 patients with epilepsy of various etiologies who had been or were currently, exposed to vigabatrin and manifested vigabatrin-attributed field loss. Group II comprised eight patients with epilepsy who had been or were currently, exposed to vigabatrin and manifested normal visual fields. Two additional patients exposed to vigabatrin exhibited equivocal visual fields and therefore could not be categorized in either Group I or II. Group III comprised 14 patients with epilepsy who had never been exposed to vigabatrin and who, at the time of the study, were receiving carbamazepine monotherapy. Carbamazepine is an anti-epileptic drug; the primary mechanism of action is believed to be the blockade of voltage-dependent sodium channels. The patients in Group III therefore served as the control for the effects of GABA modulation. Group IV comprised 20 clinically normal individuals who did not have epilepsy and who had not been exposed to antiepileptic drugs. These individuals served as a basis for the creation of appropriate confidence limits for normality for the results from the retinal imaging. Group V comprised seven patients with epilepsy who were included in the study after the data for the remaining four groups had been analyzed, and it had become apparent that patients in Groups I and II had frequently been treated with the antiepileptic drug sodium valproate before, or as combination therapy with, vigabatrin. Valproate has a mild GABAergic action believed to result from inhibition of GABA-transaminase and of succinic semialdehyde dehydrogenase and from the stimulation of benzylglutamic acid dehydrogenase which synthesizes GABA. The patients in Group V had been treated with valproate monotherapy and served, as a post hoc control, for those patients in Group I who had been treated with valproate.

All patients were recruited from the Welsh Epilepsy Unit, University Hospital of Wales, Cardiff, and the normal individuals from the University Hospital of Wales and from the Eye Clinic, Cardiff School of Optometry and Vision Sciences, Cardiff University. The participants were matched as closely as possible in age within and between the respective groups. As far as possible, patients were matched for age at onset, and duration, of epilepsy.

All participants had undergone ocular examination and conformed in each eye to rigid inclusion criteria, including a distance refractive error less than or equal to 5 diopters mean sphere and less than 2.5 diopters cylinder; open angles, and clear ocular media; no optic nerve head or fundal abnormalities characteristic of known disease; no previous ocular surgery or trauma; no history of diabetes mellitus and no family history of glaucoma. All participants manifested a visual acuity of 20/30 or better in each eye and an intraocular pressure of 21 mm Hg or less.

The participants attended two further visits. At one visit, they underwent visual field examination of the right eye. At the other, they underwent retinal imaging in the same eye. The order of the imaging and perimeter visits was randomized between individuals.

Perimetry

The visual field examination was performed with the Humphrey Visual Field Analyzer 750 (Carl Zeiss Meditec, Dublin, CA). Three-zone, age-corrected suprathreshold perimeter was undertaken with the Full Field 135 Point Screening Program, followed by threshold perimeter undertaken with Program 30-2 and the FASTPAC strategy. The appropriate refraction, corrected for the viewing distance of the perimeter bowl, was used during the examination of the central field. No correction was used for the examination beyond 30° from fixation. Patients were given frequent rest periods throughout each perimetric examination and a break of 15 to 30 minutes between examinations.

If either of the visual field examinations for any given patient were inconclusive, the corresponding examination was repeated at a subsequent visit. One patient with an unequivocal normal field derived by the Full Field 135 Point Screening Program was unable to complete Program 30-2.

Each participant in the five groups exhibited stable fixation for each perimetric examination, as indicated by the response to the gaze tracker and the responses to the fixation loss catch trials. The incorrect responses to the false-positive catch trials were also within the normal range (<30%) for all participants. The incorrect responses to the false-negative catch trials were within the normal range (<30%) for all individuals in Groups II through V. In Group I, two patients exhibited incorrect responses beyond the normal range for the Full Field 135 Point Screening Program, one participant for Program 30-2, and one for both programs.

Imaging

The imaging visit consisted of retinal imaging with OCT (StratusOCT, Carl Zeiss Meditec) and SLO with the Heidelberg Retina Tomograph II (HRT; Heidelberg Engineering, Dossenheim, Germany).

For OCT, each participant first underwent the Fast Optic Disc scan, centered on the optic disc, from which the vertical diameter of the optic nerve head was obtained. The participants then underwent three separate 360° circular scans, centered on the optic disc, using the Proportional Circle scan incorporating a scan radius that corresponded to the vertical diameter of the optic nerve head, thereby accounting for between-subject differences in the size of the optic nerve head. The macula was then separately imaged using the Macular Thickness Map scan and the Fast Macular Thickness Map scan. The two types of Macular Thickness Map scan were undertaken to determine whether the Fast Macular Thickness Map scan exhibited equivalent sensitivity and specificity relative to the longer acquisition time and increased resolution of the Macular Thickness Map scan.

The contralateral eye was occluded and participants fixated on the internal fixation target. The 2-offset and polarization were optimized before each Proportionate Circle and Macular Thickness Map scan was acquired. All scans exhibited the requirements of a signal-to-noise ratio greater than 25 dB and at least 90% good-quality A-scans. The images were then each analyzed by StratusOCT software version 3.0.

For SLO, the corneal radius was determined before imaging with a keratometer (Bausch & Lomb, Rochester, NY) to correct the images for ocular magnification. Three separate scans of the optic nerve head, and the immediate surrounding retina, were automatically obtained by the HRT software which then computed the mean of the three scans to form the output topographic image and the SD of the mean to ascertain the quality of the resulting mean image. The field size was 15° × 15°.

The participants fixated on the internal fixation target. The SD of the mean was ±10 μm in 9 of the 55 participants, between 11 and 20 μm in 36, between 21 and 30 μm in 9 participants, and 57 μm in the remaining participant in Group III. The contour line was drawn by a senior ophthalmologist (IAC) trained to fellowship standard in glaucoma and highly experienced in optic nerve head assessment and in the drawing of the contour line with the HRT, who was masked to the purpose and design of the study. The images were then analyzed by HRT software version 1.6.

The order of the imaging modality was randomized between the participants. The right eye of each participant was dilated with 0.5% tropicamide before imaging, to ensure a minimum pupil diameter of 5 mm.

Analysis

The primary analysis was undertaken on the results from the patients in Groups I through IV. After completion of the data collection for the groups, the visual field results from each participant were evaluated by
RESULTS

The respective biographical data (group mean and SD) for each of the five groups are listed in Table 1. At the time of the study, six patients in Group I and one patient in Group II were being treated with vigabatrin. The mean duration of vigabatrin therapy was greater in Group I than in Group II \((P = 0.049)\), but the mean cumulative dose of vigabatrin was similar between the two groups \((P = 0.337)\).

In the patients in Group III, the mean period of monotherapy with carbamazepine was 1.0 ± 1.2 years (SD) with a minimum period of 6 months. Five of the 14 patients had been on monotherapy throughout their clinical care. Two patients had each been treated with sodium valproate for 4 years and one patient with the antiepileptic drug phenytoin for 6 years. The remainder had received a variety of non-GABAergic antiepileptic drugs that had been withdrawn due to intolerance or ineffectiveness after short periods ranging from 12 days to 5 months. The mean duration of carbamazepine therapy was 6.1 ± 6.4 years, and the mean cumulative dose was 1.19 ± 1.3 kg (SD).

The age of the patients was similar between the four groups \((P = 0.847)\). The apparent difference in the duration of epilepsy between the patients in Groups I and II and those in Group III did not reach statistical significance \((P = 0.430)\).

Six of the seven patients in Group V had received valproate monotherapy throughout their clinical care. The seventh patient had received the antiepileptic drug lamotrigine as add-on therapy for approximately 5 months, 6 years previously. The mean duration of valproate therapy was 7.9 ± 3.6 years, and the mean cumulative dose was 3.44 ± 2.2 kg.

Optical Coherence Tomography

The average retinal nerve fiber layer thickness for the complete 360° scan for each participant as a function of group is given in Figure 1. All patients with vigabatrin-attributed visual field loss exhibited an abnormal retinal nerve fiber layer thickness beyond the lower 95% confidence limit for normality \((i.e., 100\% \text{ sensitivity at } 100\% \text{ specificity})\). Three of the eight patients exposed to vigabatrin and manifesting normal visual fields exhibited an apparently abnormal nerve fiber layer thickness.

Average retinal nerve fiber layer thickness for the complete 360° scan varied across Groups I through IV \((P < 0.001; \text{ Table 2})\). The mean average thickness in Group I, 64.8 μm, was attenuated relative to that of Group II, 97.1 μm \((P < 0.001);\) Group III, 101.5 μm \((P < 0.001);\) and Group IV, 110.6 μm \((P < 0.001)\). Given the limited size of the study sample and the tendency for an increased likelihood of a Type I statistical error resulting from the multiple comparisons of means, there was some evidence to suggest that the mean average thickness in Group II was attenuated relative to that of Group IV \((P < 0.022)\). However, this latter outcome was influenced by the two patients in Group II with an average thickness lying outside the 95% confidence limits. The trend in the average thickness between Groups I and II was repeated for each of the superior, inferior, and nasal sectors (Table 2).

The average nerve fiber layer thickness for the complete 360° scan in patients exposed to vigabatrin as a function of the Mean Sensitivity derived with Program 30-2 is shown in Figure 2 and as a function of duration of therapy with vigabatrin and of a cumulative dose of vigabatrin in Figure 3.
All patients, regardless of group, exhibited a weighted mean macular thickness within the 95% confidence limits of normality for either type of scan derived from the participants in Group IV. The group means for the weighted mean macular thickness in the Fast Macular Thickness Map scan and in the Macular Thickness Scan did not differ across Groups I through IV for either type of scan \((P = 0.086)\) and \((P = 0.086)\), respectively.

Of the two patients exposed to vigabatrin who exhibited equivocal visual fields, one manifested an abnormal nerve fiber layer thickness and a normal macular thickness. The other manifested normal nerve fiber layer and macular thicknesses.

**Scanning Laser Ophthalmoscopy**

Ten of the 13 patients with vigabatrin-attributed visual field loss exhibited a mean nerve fiber layer thickness derived by SLO beyond the 95% confidence limits of normality (i.e., 76.9% sensitivity at 100% specificity; Fig. 4). Two of the eight patients exposed to vigabatrin and manifesting normal visual fields exhibited an apparently abnormal nerve fiber layer thickness.

The mean nerve fiber layer thickness derived by SLO (Table 3) varied across Groups I to IV \((P < 0.001)\). The mean Mean Thickness in Group I, 0.126 ± 0.05 (SD) was attenuated relative to that of Group II, 0.210 ± 0.10 mm \((P < 0.034)\); Group III, 0.290 ± 0.10 \((P < 0.001)\); and Group IV, 0.260 ± 0.06 mm \((P = 0.001)\). The trend in the overall thickness between Groups I and II for each of the six sectors was less convincing and not as profound as the sector analysis for OCT (Table 2).

Of the two patients exposed to vigabatrin who exhibited equivocal visual fields, one manifested an abnormal and the other a normal nerve fiber layer thickness.

**DISCUSSION**

The results provide evidence of an attenuated retinal nerve fiber layer thickness in patients with vigabatrin-attributed visual field loss. Moreover, the sensitivity and specificity of the digital imaging techniques used in the study, particularly that of OCT, combined with the objective nature and relatively short chair time, suggest that the technique may be considered in clinical practice for the assessment of vigabatrin-attributed damage. In addition, the technique is also advocated for the evaluation of potential structural damage to the retina by ex-
isting GABAergic antiepileptic drugs and for those in Phase III studies.

The visual electrophysiology associated with vigabatrin is complex but suggests a retinal rather than a cortical origin for vigabatrin-attributed field loss. Vigabatrin is associated with a reduced Arden Index of the electrooculogram (EOG) and abnormalities of the electroretinogram (ERG) including reduced cone b-wave, a decreased amplitude of the 30-Hz flicker response, and abnormalities in photopic and scotopic oscillatory potentials. Separation of the electrophysiological effects due to vigabatrin therapy from those associated with vigabatrin-attributed damage, implicates an abnormal cone function in association with the field loss. However, although the latencies of the photopic a-wave and of the 30 Hz flicker a-wave and the 30 Hz flicker a-b amplitude yield encouraging sensitivities for the detection of at least severe vigabatrin-attributed field loss, the accompanying specificities are not sufficiently high to justify implementation of the technique. Wide-field multifocal electrotoretinography may yield better outcomes in this regard. The presence of functional abnormality at the fovea, such as reduced contrast sensitivity and abnormal color vision in patients exposed to vigabatrin is also equivocal and, therefore, measurement of these functions cannot be used to indicate vigabatrin-attributed field loss.

All patients in Groups I and II had received a variety of antiepileptic drugs encompassing the complete range of available therapies. However, eight of the 13 patients with vigabatrin-attributed visual field loss had been treated with sodium valproate before therapy with vigabatrin and four of these eight had received combination therapy of valproate and vigabatrin. The mean duration of therapy with valproate in this group was 10.0 ± 6.2 years. Six of the eight patients had been treated with valproate for nine years or more. In contrast, only two of the eight patients in Group II had received valproate: one for almost 5 years before therapy with vigabatrin and the other for 16 years of which 11 years included combination therapy with vigabatrin. One patient in Group II received valproate after withdrawal of vigabatrin. It is not possible to attribute, unequivocally, the attenuation of the nerve fiber layer to vigabatrin. Nevertheless, the evidence for a purely vigabatrin etiology is persuasive. The evidence from the study is three fold. Firstly, all patients in Group I exhibited field loss unequivocally characteristic of vigabatrin irrespective of exposure to valproate. Second, the two patients with long-term exposure to valproate in Group II both exhibited normal fields. Finally, all seven patients in Group V receiving valproate monotherapy exhibited a nerve fiber layer thickness well within the normal range by both OCT (group mean 110.0 ± 7.7 μm [SD]) and SLO (group mean 0.273 ± 0.06 mm [SD]). The evidence from the literature is also convincing. Characteristic vigabatrin-attributed visual field loss has been observed with vigabatrin monotherapy and, in the most authoritative study of valproate monotherapy and visual function, involving 32 patients treated for a mean duration of 6 years and using a daily dose between 1000 and 2000 mg, visual acuity, color vision, central field, and scotopic and photopic ERGs were all normal.

The drug history of the patients in Groups I and II is believed to reflect the local idiosyncrasy of the prescribing practice in the Welsh Epilepsy Unit during the early to mid 1990s when valproate was prescribed as the drug of first choice for all types.
Retinal nerve fiber layer thickness derived by SLO

![Retinal nerve fiber layer thickness derived by SLO](image)

**Table 3.** The Probability Values for the Comparison of the Mean Overall RNFL Thickness with the Mean Sector RNFL Thickness Derived by SLO

<table>
<thead>
<tr>
<th>Group Comparison</th>
<th>360°</th>
<th>Superior Nasal</th>
<th>Superior Temporal</th>
<th>Nasal</th>
<th>Temporal</th>
<th>Inferior Nasal</th>
<th>Inferior Temporal</th>
</tr>
</thead>
<tbody>
<tr>
<td>I vs. II</td>
<td>$P = 0.054$</td>
<td>NS</td>
<td>NS</td>
<td>$P = 0.031$</td>
<td>$P = 0.026$</td>
<td>NS</td>
<td>$P = 0.032$</td>
</tr>
<tr>
<td>I vs. III</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
<td>NS</td>
<td>$P = 0.003$</td>
<td>$P = 0.004$</td>
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<tr>
<td>I vs. IV</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
<td>$P = 0.001$</td>
<td>$P &lt; 0.001$</td>
<td>$P = 0.046$</td>
<td>$P = 0.023$</td>
<td>$P = 0.021$</td>
</tr>
<tr>
<td>II vs. III</td>
<td>NS</td>
<td>$P = 0.028$</td>
<td>NS</td>
<td>$P = 0.019$</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>II vs. IV</td>
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<td>NS</td>
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<td>III vs. IV</td>
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</table>
The mean average nerve fiber layer thickness measured by OCT exhibits an apparent floor effect at approximately 47 μm. However, it should be noted that the papillomacular bundle of ganglion cell fibers is seemingly unaffected by vigabatrin and thus will contribute to the average value for the nerve fiber layer thickness. The minimum individual recorded thickness for the thinnest sector, the nasal sector was 30 μm.

The retinal nerve fiber layer thickness decreases with increasing eccentricity from the optic nerve head. Two concepts exist for the selection of a circular scan for OCT. The first advocates a fixed diameter circular scan of 3.46 mm. This diameter is large enough to prevent any overlap with the optic nerve head. The choice of the increment is based on an increment of the vertical disc diameter; in this instance, unity. Such an approach overcomes the variation in the size of the optic nerve head. The choice of the increment is arbitrary. A scan radius based on an increment of unity yielded a mean normal average nerve fiber layer thickness of 110.6 μm. A scan radius closer to the optic nerve head (i.e., an increment of less than unity) would have yielded a thicker measure of the retinal nerve fiber layer which would have enabled a greater measurement range. The use of a scan radius based on an increment of unity is highly dependent on the axial length and, to a lesser extent, on the refractive power of the eye being imaged and does not account for variation in optic disc size within the population. A fixed-diameter scan therefore measures the nerve fiber layer thickness closer to the optic disc border in larger discs than in smaller ones.

The second approach, adopted in the present study, utilizes a scan radius based on an increment of the vertical disc diameter; in this instance, unity. Such an approach overcomes the variation in the size of the optic nerve head. The choice of the increment is arbitrary. A scan radius based on an increment of unity yielded a mean normal average nerve fiber layer thickness of 110.6 μm. A scan radius closer to the optic nerve head (i.e., an increment of less than unity) would have yielded a thicker measure of the retinal nerve fiber layer which would have enabled a greater measurement range. The use of a scan radius based on an increment of unity would be appropriate for the follow-up of children and adolescents.

The normal macular thickness in all patients in Groups I and II indicates that, within the resolution of the OCT, vigabatrin was not associated with a disturbance of the macula. There was no evidence of epiretinal membrane formation within the patients in Groups I or II. SLO was not used to evaluate the macula because, at the time of the study, the software permitting evaluation of the macula was not commercially available.

In summary, digital imaging of the retina by two different optical techniques, OCT and SLO, yielded an attenuated retinal nerve fiber layer thickness for patients with vigabatrin-attributed visual field loss. Macular thickness was normal by OCT. Assessment of retinal nerve fiber layer thickness, particularly by OCT, is a clinically viable indicator of vigabatrin-attributed damage and may be considered as an adjunct to the assessment of all adult patients exposed to vigabatrin, particularly the learning disabled and those in whom the visual field result is equivocal. Wherever possible, it should also be considered for children exposed to vigabatrin.

References


