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# Evolution of visual field loss over ten years in individuals taking vigabatrin

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## KEYWORDS

Vigabatrin;  
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tomography

## Summary

**Purpose:** Vigabatrin-associated visual field loss (VAVFL) occurs in around 45% of exposed people. It is generally accepted that, once established, VAVFL is stable and does not progress with continued VGB use. Most studies have, however, only followed people for short periods. We assessed the evolution of VAVFL over a ten-year period of continued VGB use.

**Methods:** From a group of 201 vigabatrin-exposed individuals with epilepsy, fourteen individuals were identified who were currently taking vigabatrin. All individuals had at least ten years exposure to vigabatrin. Individuals underwent several visual field examinations using Goldmann perimetry between Test 1 (first recorded examination) and Test 2 (most recent examination). All visual field results were analysed and quantified retrospectively by one investigator.

**Results:** 174 visual fields from the fourteen participants were available. The average follow-up period was 128 months. The prevalence of VAVFL increased from 64% at Test 1 to 93% at Test 2. The visual field size was significantly smaller at Test 2 compared to Test 1. All subjects showed a trend for decreasing visual field size with increasing cumulative vigabatrin exposure, when all fields for an individual were taken into account. There was a high degree of variability in visual field size between successive test sessions.

**Conclusions:** VAVFL progresses with continued vigabatrin exposure over a ten-year period. Progression may be slow and difficult to detect because of the high degree of variability in visual field size between successive test sessions. New techniques are needed to monitor the effects of vigabatrin retinotoxicity in people who continue vigabatrin therapy.

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## Introduction

Exposure to the antiepileptic drug vigabatrin (VGB) is associated with the development of visual field loss in around 45% of people (Maguire et al., 2010). It is generally accepted that, once established, vigabatrin-associated visual field loss (VAVFL) is stable and does not progress with continued VGB use (Paul et al., 2001). Several follow-up studies of individuals who continue VGB have shown no progression of VAVFL over time (Lawden et al., 1999; Nousiainen et al., 2001; Paul et al., 2001; Graniewski-Wijnands and van der Torren, 2002; Schmidt et al., 2002; Best and Acheson, 2005) (Table 1). In addition, increasing cumulative VGB exposure (Kalviainen et al., 1999; Nousiainen et al., 2001; Newman et al., 2002; Nicolson et al., 2002; Kinirons et al., 2006) and longer duration of VGB exposure (Nousiainen et al., 2001; Comaish et al., 2002; Kinirons et al., 2006; Newman et al., 2002; Vanhatalo et al., 2002) were not found to be associated with increased risk of VAVFL, further suggesting that VGB retinotoxicity does not show a progressive evolution with continued use.

Conversely, other studies have reported that higher cumulative VGB exposure (Lawden et al., 1999; Manuchehri et al., 2000; Hardus et al., 2001; Malmgren et al., 2001; Frisen, 2004), and longer duration of therapy (Lawden et al., 1999; Hardus et al., 2001; Malmgren et al., 2001; Toggweiler and Wieser, 2001; Schmitz et al., 2002) are associated with increased risk of VAVFL. In addition, occasional reports have arisen of progression of VAVFL with continued VGB use (Lawden et al., 1999; Hardus et al., 2000, 2003; Clayton et al., 2010) (Table 1).

Studies of the evolution of VAVFL in people continuing VGB therapy have followed participants for short periods of time (Table 1). In one case report, which illustrated the evolution of visual field size with continued VGB exposure over a longer period, the visual field size showed a significant decrease after ten years of VGB use, suggesting that VAVFL may progress in some people after many years of VGB exposure (Clayton et al., 2010).

Understanding the evolution of VAVFL with continued VGB exposure over a long period of time is essential for optimal management, enabling decisions to be made about the risks and benefits of continued therapy.

We assessed the evolution of VAVFL over a ten year period in people taking VGB. We hypothesised that VAVFL progresses with increasing cumulative VGB exposure.

## Methods

The project was approved by the local institutional ethics committee. All participants provided written, informed consent.

## Subjects and recruitment

201 VGB-exposed individuals with epilepsy were recruited from specialist National Health Service clinics of the National Hospital for Neurology and Neurosurgery as part of a large study of VAVFL (Clayton et al., 2011). From this cohort, all individuals who were *currently* being treated with VGB were identified and were recruited to take part in this study. Fourteen individuals were identified in total. All 14

**Table 1** Summary of follow-up studies reporting changes in the visual field with continued VGB exposure.

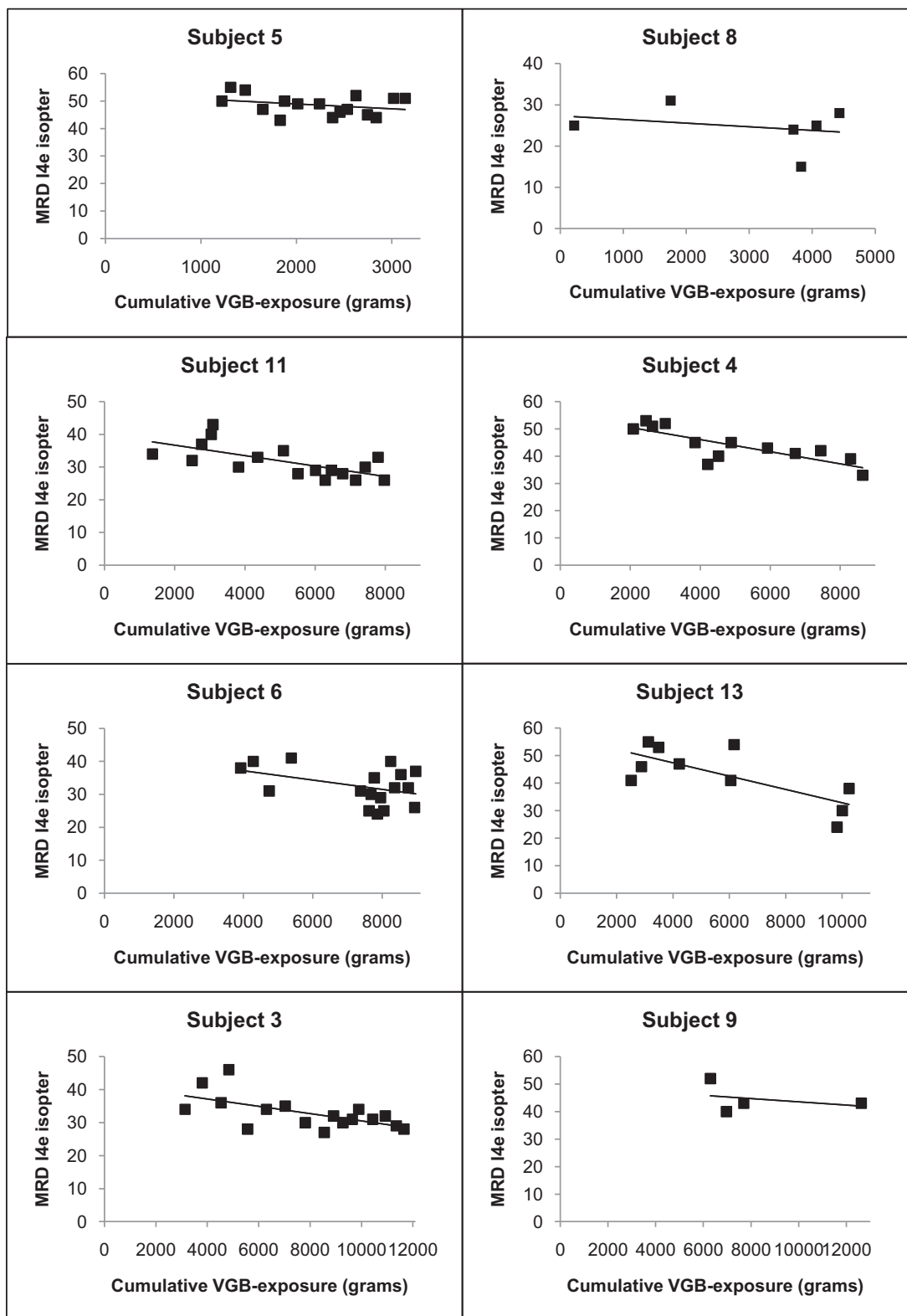
| Reference                                     | Number of participants | Follow-up (months) | Overall conclusion | How the data were analysed                   |
|---|------------------------|--------------------|--------------------|--|
| Clayton et al. (2010)                         | 1                      | 120                | Progression        | Observation                                  |
| Kinirons et al. (2006)                        | 41                     | 6–67               | No progression     | Criteria <sup>a</sup>                        |
| Hardus et al. (2000) <sup>c</sup>             | 11                     | 13–61              | Progression        | Statistical test <sup>b</sup>                |
| Best and Acheson (2005)                       | 16                     | 18–43              | No progression     | Observation<br>Statistical test <sup>b</sup> |
| Lawden et al. (1999)                          | 1                      | 39                 | No progression     | Observation                                  |
| Nousiainen et al. (2001)                      | 26                     | 4–38               | No progression     | Observation<br>Statistical test <sup>b</sup> |
| Schmidt et al. (2002)                         | 4                      | 12–24              | No progression     | Observation<br>Statistical test <sup>b</sup> |
| Graniewski-Wijnands and van der Torren (2002) | 9                      | 18                 | No progression     | Observation                                  |
| Paul et al. (2001)                            | 15                     | 12                 | No progression     | Observation<br>Statistical test <sup>b</sup> |
| Lawden et al. (1999)                          | 1                      | 11                 | Progression        | Observation                                  |

Observation = progression of VAVFL was determined from either direct observation and qualitative evaluation of serial visual field data, or from observation of serial quantitative measure of VAVFL, typically plotted in a graphical format (e.g. serial MRD measurements shown graphically in Clayton et al. (2010)).

<sup>a</sup> when analyzing progression or recovery of visual fields, the authors considered a change in MRD of  $\leq 5\%$  as stable, of 6–10% as indeterminate, and of  $>10\%$  as pathologic change.

<sup>b</sup> Either a paired-samples *T*-test or a Wilcoxon Signed Rank Test was used to determine a statistically significant difference in visual field size between two predefined test points.

<sup>c</sup> Also Hardus 2003 (Hardus et al., 2003) reports progression of VAVFL in five people who were included in the earlier report (Hardus et al., 2000) of 11.



**Figure 1** Visual field size in relation to cumulative VGB exposure for each Subject: Graphs for each individual showing the visual field size in mean radial degrees (MRD) at each successive examination (represented by ■), in relation to the cumulative vigabatrin (VGB) exposure at that time. Graphs are numbered according to the subject number, and are shown in order of increasing cumulative VGB exposure. A linear trendline, derived from all visual field results, was added to each individual’s data. The slope of the trendline was determined using  $y = mx + b$ , where  $m$  = the slope of the line.

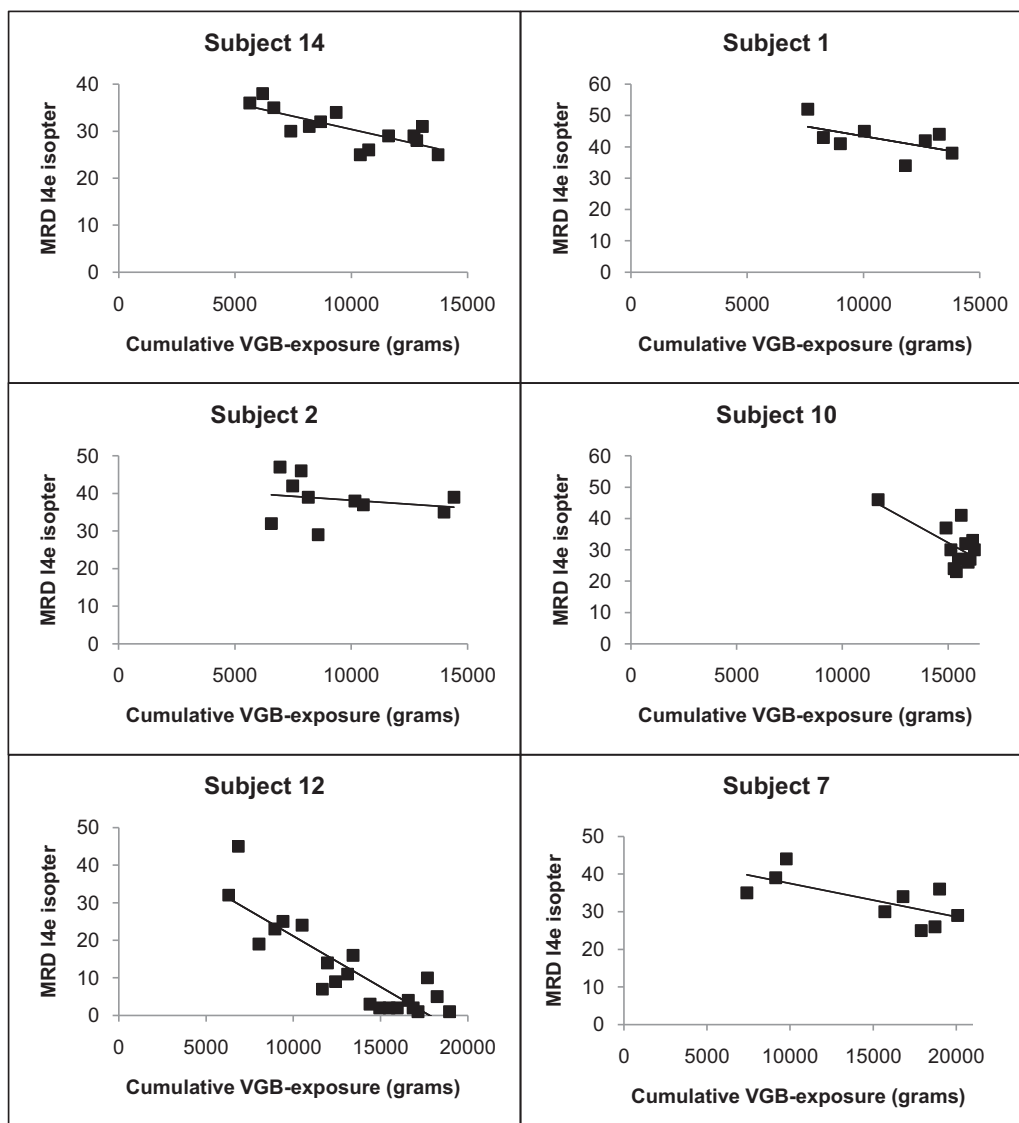


Figure 1 (Continued)

had originally participated in a study of VAVFL commencing in 1999 (Newman et al., 2002). All were under active neuro-ophthalmological follow-up because of VGB use. None had a history of ocular disease, a family history of glaucoma, or a history of surgery to the eye, orbit or brain. Data on VGB exposure were obtained from the medical notes.

**Perimetry**

All subjects were examined on at least one occasion by a single researcher (LMC) using Goldmann kinetic perimetry. Monocular vision was examined, with the non-tested eye fully occluded, using V4e, I4e and I2e stimuli. Appropriate full aperture spectacle correction was used for examination of the central 30° of the visual field. Fixation was monitored by direct visualisation of the fixating eye.

Other examinations of the visual field were performed as part of routine neuro-ophthalmological assessment related to VGB exposure, and as part of other studies of VAVFL

(Newman et al., 2002). These examinations were undertaken by skilled operators according to clinical protocols.

Visual fields obtained by LMC were assessed for their reliability during the examination. Unreliable fields were determined based on false positive responses, fixation losses and highly variable responses to the same stimulus. Visual fields obtained by other examiners were reviewed retrospectively by LMC. The reliability of the visual field was determined based on the original operator’s comments on the visual field chart.

**Data analysis**

Visual fields obtained from the right eye were analysed. Only data from one eye were analysed as it is accepted that VAVFL is characterised by a symmetrical contraction of the visual field (Wild et al., 1999). Visual fields were quantified using mean radial degrees (MRD) which was also used in the original study (Newman et al., 2002). Using this method

the radial distance in degrees of the 14e isopter was measured from fixation, at 12 points, 30° apart. The MRD was determined by calculating the average radial distance in degrees from the 12 points. All assessments were quantified and analysed by one researcher.

The cumulative VGB exposure at the time of each visual field examination was determined, and a graph of cumulative VGB exposure and MRD, at successive examinations over the follow-up period, was plotted for each person (Fig. 1). A linear trendline, derived from all visual field results, was added to each subject's data (Fig. 1). The slope of the trendline was determined using  $y = mx + b$ , where  $m$  = the slope of the line.

For further analysis, the first recorded visual field assessment whilst on VGB (Test 1) and the latest recorded assessment whilst still taking VGB (Test 2) were considered. Visual fields taken during Test 1 and Test 2 were classified as normal or showing mild, moderate or severe VAVFL according to described criteria (Wild et al., 1999). Follow-up time was defined as the time in months between Test 1 and Test 2.

## Results

### Subject data

176 visual field tests (median number of examinations per subject = 13) from fourteen people (64% male) were available. Two visual field tests were excluded (one each from participant 5 and 7), as the operator had indicated that the results were unreliable, leaving 174 visual field tests available for analysis. One individual included in this study (Subject 12) has previously been reported (Clayton et al., 2010).

Details of VGB exposure, concomitant antiepileptic drug exposure, seizure frequency, follow-up time and visual field size for each participant are shown in Tables 2 and 3.

### Analysis of visual field data at Test 1 and Test 2

#### Visual field classification

At Test 1, 9/14 (64.3%) individuals had VAVFL. At Test 2, 13/14 (92.9%) individuals showed VAVFL. Six individuals had progressed by at least one class (e.g. from normal to mild VAVFL). Seven remained within the same class. One individual (Subject 2) showed an improvement from moderate to mild VAVFL, but only when considering data at Test 1 and Test 2 (Table 2).

#### Visual field size

A Wilcoxon Signed Rank Test showed that the visual field at Test 2 was significantly smaller than at Test 1 ( $z = -2.48$ ;  $p < 0.05$ ; Table 2). The average difference in visual field size between Test 1 and Test 2 was 7.5 MRD.

#### Individuals with normal visual fields at Test 1

Five people (Subjects 1, 4, 5, 9 and 10) had normal visual fields at Test 1 (Table 2). At Test 2 one showed a normal visual field according to the classification criteria, two showed mild VAVFL and two showed moderate VAVFL.

## Analysis of all available visual field data

### Evolution of VAVFL

A graph of cumulative VGB exposure and MRD at successive examinations was plotted for each subject and a linear trendline was added. The trendline showed a negative trend for all subjects, suggesting an overall decrease in the visual field size with increasing cumulative VGB exposure. Fluctuations in visual field size were seen for all subjects (Fig. 1).

### Rate of change of visual field size

The rate of change of the visual field size was determined for each subject from the slope of the trendline and ranged from 0.4 to 3.7 MRD loss per kilogram of cumulative VGB dose (Table 2).

## Discussion

This is the longest follow-up study of VAVFL in people continuing VGB therapy, and shows the evolution of VAVFL with increasing VGB exposure. The results suggest VAVFL progresses with continued VGB use. The prevalence of VAVFL increased from 64% at Test 1 to 93% at Test 2. All people included in the study showed a trend for decreasing visual field size with increasing cumulative VGB exposure when all fields for a subject were taken into account (Fig. 1). Our results concur with a previous report of an increase in the percentage visual field loss with continued VGB use over a 13–61 month follow-up period in 11 individuals (Hardus et al., 2000). The majority of studies, however, have reported that once established, VAVFL is stable and does not progress further with continued VGB use (Lawden et al., 1999; Nousiainen et al., 2001; Paul et al., 2001; Graniewski-Wijnands and van der Torren, 2002; Schmidt et al., 2002; Best and Acheson, 2005). The conflicting evidence regarding the evolution of VAVFL with continued VGB exposure may be due to a number of factors. Good, prospective data on the course of VAVFL are lacking (Kinirons et al., 2006), and most studies, including our study, rely on retrospective analysis of visual field data acquired by different examiners over many years. Perimetry also has inherent limitations which may make it impractical to detect changes in the visual field over time in VGB-exposed individuals, particularly if these changes are small and follow-up periods are short.

### Problems with measuring the visual field

In many people with epilepsy, perimetric results may be unreliable and repeated testing is often needed, after which results can still prove difficult to interpret (Wild et al., 2006). In this study, evaluation of serial visual field tests showed a variable degree of fluctuation above and below the trendline (Fig. 1). These fluctuations are likely to represent "normal" variability that is not related to VGB-associated pathological change, but are the result of both subject-related and examiner-related factors (Parrish et al., 1984).

Subject-related factors influencing the recorded visual field include fatigue (Wild et al., 1991), reaction time (Becker et al., 2005), an inadequate explanation or understanding of the task (Parrish et al., 1984; Kutzko et al., 2000) and a "learning effect" whereby individuals show an

**Table 2** VGB exposure and visual field data for each Subject.

| Subject (number of visual fields) | Maximum daily VGB dose (g) | Cumulative VGB exposure (g) |        | Duration of therapy (months) |            | Follow-up (months) | Test 1     |                | Test 2      |                | Rate of change of MRD/kg of VGB exposure <sup>b</sup> |
|-----------------------------------|----------------------------|-----------------------------|--------|------------------------------|------------|--------------------|------------|----------------|-------------|----------------|---|
|                                   |                            | Test 1                      | Test 2 | Test 1                       | Test 2     |                    | MRD        | Classification | MRD         | Classification |   |
| 1 (8)                             | 2.5                        | 7606                        | 13,806 | 122                          | 230        | 108                | 52         | Normal         | 38          | Mild           | -1.3  |
| 2 (10)                            | 2.0                        | 6570                        | 14,427 | 84                           | 213        | 129                | 32         | Moderate       | 39          | Mild           | -0.4  |
| 3 (17)                            | 2.0                        | 3134                        | 11,654 | 45                           | 185        | 140                | 34         | Moderate       | 28          | Moderate       | -1.1  |
| 4 (13)                            | 2.0                        | 2086                        | 8640   | 35                           | 144        | 109                | 50         | Normal         | 33          | Moderate       | -2.2  |
| 5 (16)                            | 0.5                        | 1220                        | 3141   | 58                           | 190        | 132                | 50         | Normal         | 51          | Normal         | -1.8  |
| 6 (16)                            | 3.0                        | 4286                        | 8961   | 43                           | 170        | 127                | 38         | Mild           | 37          | Mild           | -1.4  |
| 7 (9)                             | 3.0                        | 7398                        | 20,085 | 91                           | 230        | 139                | 35         | Moderate       | 29          | Moderate       | -0.9  |
| 8 (6)                             | 2.0                        | 221                         | 4432   | 5                            | 139        | 134                | 25         | Moderate       | 28          | Moderate       | -0.9  |
| 9 (4)                             | 2.0                        | 6299                        | 12,627 | 112                          | 216        | 104                | 52         | Normal         | 43          | Mild           | -0.6  |
| 10 (13)                           | 3.0                        | 11,629                      | 16,247 | 121                          | 235        | 114                | 46         | Normal         | 30          | Moderate       | -3.7  |
| 11 (17)                           | 1.5                        | 1367                        | 7154   | 20                           | 164        | 144                | 34         | Moderate       | 26          | Moderate       | -1.6  |
| 12 (21)                           | 3.0                        | 6297                        | 18,950 | 49                           | 197        | 148                | 32         | Moderate       | 1           | Severe         | -2.7  |
| 13 (10)                           | 2.0                        | 2516                        | 10,250 | 36                           | 162        | 126                | 41         | Mild           | 38          | Mild           | -2.4  |
| 14 (14)                           | 2.0                        | 5632                        | 13,106 | 83                           | 216        | 133                | 36         | Mild           | 31          | Moderate       | -1.1  |
| Average (SD)                      | 2.0 (0.5–3.0) <sup>a</sup> | 4737                        | 11,677 | 64.6                         | 192 (32.4) | 127.6 (14.0)       | 39.8 (8.8) |                | 32.3 (11.3) |                |   |

VGB = vigabatrin; MRD = mean radial degrees; Test 1 = first visual field examination taken whilst on VGB; Test 2 = latest visual field examination taken whilst on VGB.

<sup>a</sup> Median (range).

<sup>b</sup> Determined from the slope of the trendline using  $y = mx + b$ , where  $m$  = the slope of the line. Note if only results at Test 1 and Test 2 are considered, some individuals would have been thought not to show any progression.

**Table 3** Clinical data for each Subject.

| Subject | Age at Test 2 (years) | All other AEDs exposed to during VGB exposure | AEDs exposed to at Test 1 and Test 2 (dose of VGB in grams) |                          | Seizure frequency at Test 1 and Test 2 <sup>a</sup> |   |
|---------|-----------------------|---|---|--------------------------|---|---|
|         |                       |   | Test 1  | Test 2                   | Test 1  | Test 2  |
| 1       | 52                    | CBZ   | VGB (2.0), CBZ  | VGB (1.5)                | Seizure free  | Seizure free  |
| 2       | 39                    | CBZ, CLN, PHT                                 | VGB (2.0), CBZ, CLN   | VGB (2.0), CBZ, CLN, PHT | Frequent nocturnal complex partial seizures         | Frequent nocturnal complex partial seizures               |
| 3       | 44                    | VPA, CBZ, OXC                                 | VGB (2.0), VPA, CBZ   | VGB (2.0), VPA, OXC, CBZ | Daily myoclonic jerks. One GTCS per week            | Daily myoclonic jerks. Three to four GTCS per month       |
| 4       | 38                    | VPA   | VGB (2.0), VPA  | VGB (2.0), VPA           | Seizure free  | Seizure free  |
| 5       | 40                    | CBZ   | VGB (0.5), CBZ  | VGB (0.5), CBZ           | Seizure free  | Seizure free  |
| 6       | 33                    | CBZ, TPM, TGB, PHB, PGB, ZON, LAC             | VGB (3.0), CBZ, TPM, TGB                                    | VGB (1.0), CBZ TPM, LAC  | 30-38 seizures per month                            | Five to six seizures per day                              |
| 7       | 46                    | CBZ, PMD, LEV, TPM                            | VGB (3.0), CBZ, PMD   | VGB (1.5), CBZ, LEV, TPM | No details <sup>b</sup>                             | Six "mild seizures" per month                             |
| 8       | 51                    | CBZ, TPM, PHB, CLB, LEV,                      | VGB (2.0), CBZ, TPM, PHB, CLB                               | VGB (2.0), CBZ, LEV, CLB | Four to five complex partial seizures per day       | Daily complex partial seizures                            |
| 9       | 53                    | GBP   | VGB(2.0), GBP   | VGB (2.0), GBP           | Data unavailable <sup>c</sup>                       | Clusters of complex partial seizures every few months     |
| 10      | 56                    | CBZ, CLB, LEV                                 | VGB (3.0), CBZ, CLB   | VGB (0.5), CBZ, CLB, LEV | Seizures every two months                           | "Unsure" (monthly seizures recorded six months before T2) |
| 11      | 49                    | CBZ   | VGB (1.5), CBZ  | VGB (1.5), CBZ           | Seizure free  | Seizure free  |
| 12      | 36                    | CBZ, GBP, TPM, LAC                            | VGB (3.0), CBZ, GBP   | VGB (3.0), CBZ, TPM, LAC | Three complex partial seizures per week             | Several complex partial seizures per week                 |
| 13      | 36                    | LEV, CLB, data missing <sup>d</sup>           | VGB (2.0), data missing <sup>d</sup>                        | VGB (2.0), LEV, CLB      | Data unavailable <sup>c</sup>                       | Seven seizures in six months                              |
| 14      | 63                    | CBZ, LEV                                      | VGB (2.0), CBZ  | VGB (2.0), CBZ           | Weekly simple partial seizures                      | Seizure free  |

AED, antiepileptic drug; CBZ, carbamazepine; CLB, clobazam; CLN, clonazepam; GBP, gabapentin; LAC, lacosamide; LEV, levetiracetam; OXC, oxcarbazepine; PHB, phenobarbital; PHT, phenytoin; PGB, pregabalin; PMD, primidone; TGB, tiagabine; TPM, topiramate; VPA, valproate. Data are taken from case notes. Recording standards have changed over the time course of VGB exposure, such that some data are unavailable.

<sup>a</sup> Seizure frequency taken from the clinic letter closest to the time that the visual field assessment was performed.

<sup>b</sup> Details of seizure frequency not provided in clinic letters from that time period.

<sup>c</sup> Clinic letters regarding seizure frequency unavailable from this time period.

<sup>d</sup> Full details of concomitant AED use during early VGB exposure period unavailable.

improvement of the visual field over subsequent test sessions related to improved performance and familiarity with the task (Heijl et al., 1989; Wild et al., 1989). In healthy people, the visual field size was found to fluctuate by up to 16% between test sessions (Ross et al., 1984). In individuals with visual impairment due to retinitis pigmentosa, the fluctuation in visual field size not related to disease progression was as high as 50% between sessions in some (Ross et al., 1984). In people with epilepsy, fluctuations in visual field size may be exaggerated. Certain antiepileptic drugs (Aldenkamp, 2001; Hesse et al., 2006), seizures, the underlying cause of the epilepsy and psychosocial factors (Meador, 2002) can impair cognition, attention and psychomotor speed, all of which are integral to performing perimetry reliably. As these factors may fluctuate over time, their influence on the recorded visual field may also fluctuate, exaggerating the normal variability between test sessions, and making it difficult to detect true pathological change (Parrish et al., 1984).

Examiner-related factors may also contribute to the variability in the recorded visual field (Berry et al., 1966; Nowomiejska et al., 2005; Ramirez et al., 2008), particularly when using a manual perimetric technique (Kolling and Wabbel, 2000). The speed and direction of movement of the light-stimulus which is used to assess the visual field is operator-dependent. Optimal rates of stimulus movement have been suggested (Greve et al., 1976; Johnson and Keltner, 1987), but the speed and technique used by an operator may be influenced by the subject's performance and ability, the time constraints of the clinical setting and the examiner's skill and experience (Johnson and Keltner, 1987; Nowomiejska et al., 2005). The instructions given by the examiner on how to perform the assessment can also affect the obtained visual field result (Kutzko et al., 2000).

### Problems with detecting and defining progression of VAVFL

Several studies of VAVFL have attempted to overcome the effects of "normal" fluctuation on detecting progression of VAVFL by using criteria to define pathological change in visual field, including a change in the visual field of  $\geq 10\%$  (Kinirons et al., 2006) or of more than 10 MRD (Newman et al., 2002; Best and Acheson, 2005). The disadvantage of using these arbitrary criteria is that they may miss small pathological changes (Kinirons et al., 2006). For example, whilst all participants in this study show a trend for progression of VAVFL when all visual field tests were considered (Fig. 1), only four (Subjects 1, 4, 10 and 12) show a decrease in visual field size of  $\geq 10$  MRD when comparing Test 1 and Test 2 (Table 2).

The small degree of change in the visual field size with increasing VGB exposure may be difficult to detect clinically if serial results are assessed subjectively for evidence of progression (Parrish et al., 1984), a method that has been utilised in some studies, or when follow-up periods are short (Table 1). Failure to detect progression of VAVFL may also relate to the analysis used in some studies. In this study, Subject 2 showed an apparent improvement in the visual field from moderate VAVFL at Test 1 to mild VAVFL at Test 2 when considering only these two time points (Table 2). When all time points were considered, however, the

trendline indicated a progressive decrease in visual field size over the follow-up period (Fig. 1). Many studies of VAVFL progression have used analysis techniques where only two visual field test points were taken into account to determine whether a change has occurred (Table 1). If any of the test points used in an analysis were significantly influenced by non-pathological variation, then the analysis may fail to detect a change in the visual field size. The present study is also subject to all of the subject- and examiner-related factors discussed; however, the advantage is that for each individual all available reliable results were used in the evaluation of progression (Fig. 1). Quantifying and graphically illustrating the visual field results from all available examinations enables detection of trends in changing visual field size (either qualitatively or by applying a trendline to the data), whilst allowing for the effect of "normal" variability.

It is important to note that the rate of progression of VAVFL appears to differ between individuals. For example, in our study, Subject 2 and Subject 12 were followed up over similar VGB exposure durations and had similar visual fields at Test 1. In the follow-up period, the average rate of loss for Subject 12 was higher (2.7 MRD/kg cumulative VGB exposure), leading to severe VAVFL, whilst Subject 2 showed a more slowly progressive course (0.4 MRD/kg cumulative VGB exposure), with the visual field size showing little change over time (Table 2; Fig. 1). The inter-individual differences in the rate of progression of VAVFL may account for some of the variation in susceptibility to VAVFL seen in individuals exposed to similar amounts of VGB. This finding may have implications for phenotyping in drug response studies of VAVFL. Current understanding of the relationship between VGB exposure and visual field loss comes from cross-sectional studies typically looking at visual field size after a given VGB exposure. The rate of change in the visual field size with increasing cumulative VGB exposure may, however, provide a stronger indicator of a person's risk of developing significant VAVFL, and may provide a more useful measure to consider in the management of people continuing VGB therapy.

At the time of Test 1, the average duration of VGB exposure was five years, and 9/14 individuals had VAVFL. We note that the true pattern of visual field loss may not be linear, and that the progression observed in the present study may not represent the pattern and rate of progression of VAVFL prior to, or subsequent to, the observation period. We have simply used one method (trendline interpolation) to illustrate progression. Prospective longitudinal studies including visual field examinations prior to VGB exposure are needed to fully elucidate the pattern of VAVFL onset and progression. In addition, including analysis of visual fields in a control group of individuals with epilepsy who have no exposure to VGB, but are matched in terms of sex, age, seizure frequency and concomitant antiepileptic drug use, may overcome subject-related fluctuations in visual field size.

In this study we have not considered the effect of increasing age on visual field size over the follow-up period. Visual sensitivity declines with increasing age (Spry and Johnson, 2001). In the first six decades of life this effect is small (Spry and Johnson, 2001). 13/14 people included in this study were less than 60 years old at the time of Test 2 (Table 2), thus any contribution of increasing age to the change in



visual field size over the follow-up period is likely to have been small.

### New methods are needed

Perimetry may not be the most appropriate tool for monitoring visual dysfunction in VGB-exposed people. New methods to assess the effects of VGB retinotoxicity are needed, particularly in those in whom perimetry is unreliable or unfeasible. Electroretinography has been explored as a potential tool to monitor VGB retinotoxicity; however, no measure has consistently shown to be associated with the presence or severity of VAVFL (Wild et al., 2006).

Peripapillary retinal nerve fibre layer thinning measured using optical coherence tomography has been suggested to be a sensitive and specific indicator of VAVFL (Lawthom et al., 2009; Clayton et al., 2011) and provides an objective tool, with highly repeatable measures in VGB-exposed individuals (Clayton et al., 2011). Owing to the limited availability of commercial optical coherence tomography, and the relatively recent suggestion for its use in the assessment of VGB-exposed people (Lawthom et al., 2009; Clayton et al., 2011), longitudinal data on changes in the peripapillary retinal nerve fibre layer with continued VGB exposure are not currently available. Further studies are needed to identify whether measures of peripapillary retinal nerve fibre layer thickness provide a suitable tool for the assessment of progression of VGB retinotoxicity and associated visual dysfunction.

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