Vigabatrin-Attributable Visual Field Defects in Patients with Intractable Partial Epilepsy

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Abstract-

Introduction: Vigabatrin (VGB) is implicated to cause visual field defects. We estimated the prevalence, described the characteristics and investigated the risk factors of VGB-attributable visual field defects.

Methods: Patients with intractable partial epilepsy under VGB add-on treatment received static perimetric examinations. Visual field charts were reviewed and interpreted using a three-grade system. Clinical features and therapeutic courses were analyzed for possible risk factors.

Results: Visual field defects in at least one eye were detected in 27 (79%) of 34 patients. In the subgroup of 27 patients with both eyes reliably tested, 16 (59%) had bilateral defect, among whom seven were severely involved and showed nasally dominant, crescent or concentric defect. Five patients had unilateral visual field defects. Four out of the 27 affected patients reported blurred vision. No statistically significant differences were noted between patients with and without visual field defects in terms of gender, age, duration or etiology of the epilepsy, and duration, maximum daily dose, or cumulative dose of VGB.

Conclusions: There was a high prevalence of VGB-attributable visual field defects. No risk factors could be identified. Routine initial and regular follow-up of visual field examination, especially that focusing within a range of central fixation to 60˚, should be performed in patients on VGB.

Key Words: Intractable partial epilepsies, Perimetry, Risk factors, Vigabatrin, Visual field defect

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INTRODUCTION

Vigabatrin (VGB) is considered one of the most effective new antiepileptic drugs developed in the mid-1980[(1)]. Its antiepileptic effect is mediated by the irreversible inhibition of gamma-aminobutyric acid (GABA)-transaminase, leading to an increase of GABA (an inhibitory neurotransmitter) concentrations in presy-

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naptic terminals within the central nervous system[2]. VGB is approved for the adjunctive management of refractory partial epilepsy, and for initial monotherapy in the management of infantile spasm. However, VGB is markedly more effective in increasing the concentration of GABA in retina than in brain[3]. During the development of VGB, the incidence of visual field loss was estimated to be 14.5/10 000 patients a year[4]. The first report of visual field abnormalities associated with the use of VGB was published in 1997[5]. Subsequent studies report a wide range of the prevalence of visual fields loss from 17 to73%[6-15]. This change also occurred in children treated with VGB[16] although the incidence may be lower[17]. Primary visual field abnormalities have been identified as concentric or predominant nasal field loss[6,14]. Some researchers believe that these defects are more frequently found in male users[14,15] or those who take cumulative doses of at least 1500 g[10], but these proposals are not widely accepted[8,9,12]. A causal relationship between VGB treatment and a specific pattern of bilateral visual field constriction were demonstrated in controlled studies[6-8,10,13,15]. Furthermore, the severity of abnormal electroretinographic findings in VGB patients is tightly correlated with the degree of visual field constriction[7]. The retinal toxicity of VGB might be genetically based and it was recommended that similar studies should be conducted in other populations with different gene pools[8]. We therefore investigate the prevalence and the characteristics of VGB-attributable visual field defects, and the risk factors for visual field defect in patients with intractable partial epilepsy and taking VGB as an add-on polytherapy. The results are comparable to those from the previous reports based on Caucasian patients.

METHODS

The epilepsy clinic in the National Cheng Kung University Hospital, Tainan, Taiwan is the solo practice of the corresponding author. The patients were consecutively registered from the beginning of the epilepsy clinic in 1988 and managed with the same diagnostic and therapeutic rationales. The demographic data and the relevant clinical information of these patients were obtained by chart review. All recruited patients had intractable partial epilepsy, which is defined as one or more clinical seizures per month despite of a therapeutic regimen of at least two antiepileptic agents in the maximal tolerable doses. Each patient had at least one electroencephalography and one computed tomography or magnetic resonance imaging examination. The etiology of epilepsy was defined as cryptogenic if there was no history of brain insult and no structural lesion in the neuroimage study. Symptomatic epilepsy referred to the presence of a structural lesion relevant to the seizures in the neuroimage study or a definite history of brain insult. VGB is indicated as an add-on therapy among patients with intractable partial epilepsy. The course of VGB use was reviewed, including the date of initiation, the methods of titration, the maximum daily dose, the date of discontinuation, and the subjective complaints in each visit. The cumulative dose of VGB was calculated from the initiation of the drug till the date of visual field examination or drug discontinuation if it was stopped before the visual field examination. These patients were referred to the department of ophthalmology in the National Cheng Kung University Hospital, where the ophthalmologic diagnosis was made with detailed ophthalmologic history of glaucoma, amblyopia, retinal detachment, the use of eyewash, ocular surgery or trauma and other eye conditions were taken into consideration. All of the review and interpretation of the results of visual field examination are done on a blind basis.

Ophthalmic exclusion criteria for patients selection included: (1) the best corrected visual acuity worse than 20/40; (2) a prior history of laser treatment or other ophthalmic surgical procedures; (3) a history of glaucoma or retinal detachment; (4) other intracranial diseases that caused visual field defect (e.g., pituitary lesions, demyelinating diseases, multiple cerebral infarctions), except for those causing a typical homonymous hemianopia.

Except the spontaneously reported visual symptoms, we made inquiries for blurred vision, flickering light, tearing, and diplopia. Each patient had ophthalmic examinations on or with (the best-corrected) visual acu-

ity, intraocular pressure, slit-lamp, ocular fundus, and visual field. Two times of visual field examinations were done with the aid of static perimetry of Oculus Field Analyzer (Twinfield, Oculus Optikgeräte Gmbh, Wetzlar-Dutenhofen, Germany) and a size III white target superimposed on 31.5 apostilb (10-candela/mm^2) white background. The 30-2 program and fast threshold strategy were applied with central fixation to 30˚ eccentrically. Reliability check-up was performed automatically during the perimetric test. A reliable test is defined as having ≤ 33% false positives, ≤ 33% false negatives, and ≤ 33% fixation losses. Each visual field examination was reviewed blindly. The presence of visual field defect and its severity were interpreted using a grading system described by Wild et al.[14] The field threshold of each detecting locations ($p<0.01$ if compared with normal age-matched subjects) was set to define the defected visual field, with the exclusion of specific patterns related to known brain pathology. The pattern of field loss was then classified into whole field loss (constricted with defect in central 5˚ radius), concentric, crescent, or patchy with its location in the superior, inferior, nasal or temporal fields. The severity of the visual field defect was graded into mild, moderate or severe according to the numbers and position of defected locations. We used the Mann-Whitney-U-Test, Fisher's Exact Test and logistic regression for the identification of risk factors associated with the occurrence of visual field defect.

RESULTS

From September 1995 to November 2002, 43 patients received VGB add-on therapy in the epilepsy clinic of National Cheng Kung University Hospital, Tainan, Taiwan were recruited for this study. Among the 43 patients, 4 patients were excluded because of poor vision due to other ophthalmic disease in 2 patients, and inability to complete the test because of mental or psychiatric handicaps in 2 patients. Another 5 patients underwent the perimetric test were excluded because of large discrepancies between both eyes. For the 34 patients who were included for the final analysis, the demographic data and the history of VGB usage were shown on Table 1. We found that 27 (79%) out of the 34 patients have visual field defects in at least one eye. In a subgroup of 27 patients whose both eyes were reliably tested, 16 (59%) had bilateral visual field defect (7 out of the 16 were severely involved). Among the rest 11 patients, 5 had unilateral visual field defects and 6 were not affected.

The reliably examined visual field charts of 61 eyes were analyzed. Seven eyes were excluded because of unacceptable loss of fixation (> 33%). The pattern and severity of visual field defects which were not ascribable

Table 1. *Demographic and other characteristics of the patients*

	With visual field defects	Without visual field defects	*P*
Number of patients	27	7	
Gender (male/female)	13/14	5/2	0.405*
Age (years)	36.36 (21.13-52.14)	31.97 (21.23-51.89)	0.166**
Duration of epilepsy (years)	21.72 (7.82-39.14)	19.89 (10.02-28.59)	0.277**
Epilepsy etiology (cryptogenic/symptomatic)	15/12	6/1	0.210*
Time between VGB initiation and visual field examination (years)***	2.1-4.8	0.5-6.3	
Duration of VGB use (years)***	4.05 (0.17-4.78)	2.72 (0.83-6.31)	0.438**
Maximum daily VGB dose (mg)***	3000 (2000-3000)	3000 (1000-4000)	0.731**
Cumulative VGB dose (g)***	4075.5 (115.5-5018.5)	2121 (581-460.95)	0.121**
Number of patients with visual complaints	7	0	0.300*

Data were presented as median (min-max).

*: Fisher's Exact Test; **: Mann-Whitney-U-Test; ***: Two patients with visual field defect and one patient without visual field defect were not included due to incomplete VGB treatment history.

to a known cause were summarized in Table 2. Concentric or whole field defect was found in 10 eyes. Eleven eyes showed a crescent defect pattern with nasal dominance (Fig.), while only two eyes with nasal sparing. In 20 eyes with mild and moderate visual field defect, the visual field defect was located superiorly or nasally in 10 eyes. All the visual field defects were peripheral except for one eye which has a scotoma extending from the blind spot. Among 34 patients, seven patients had ophthalmic complaints, including blurred vision in 3 patients, tearing in 2 patients, both blurring and tearing in 1 patient, and diplopia in 1 patient. Thus vision-related complaint (blurring) occurred in 4 (15%) of the 27 patients with visual field defect.

We compared the demographic data of patients with and without visual field defect among these 34 patients (Table 1). The gender, age, and duration of epilepsy were not significantly different. There was also no difference between cryptogenic and symptomatic etiology. Also, the difference in the duration of VGB treatment, maximum daily dose or cumulative dose did not reach statistical significance. Logistic regression was performed for the above variables, but did not contribute to the presence of VGB-attributable visual field defects.

DISCUSSION

The significance of VGB-attributable visual field

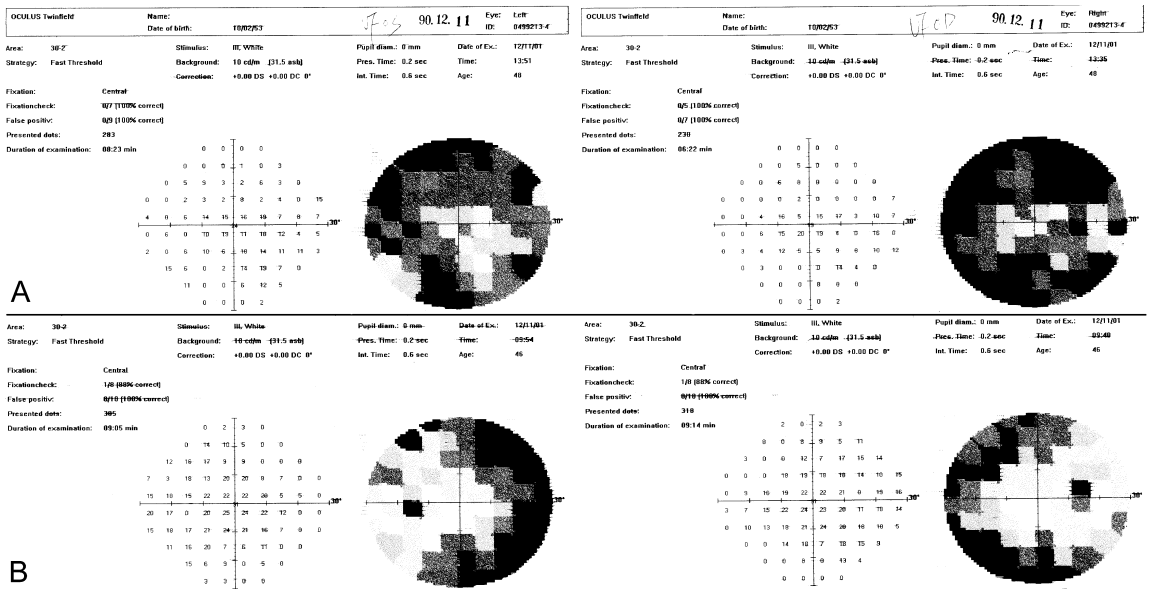

Figure. (A) Concentric visual field defect. (B) Crescent visual field defect with nasal dominance.

Table 2. *Severity and patterns of the visual field defect*

Visual field defect	Severe				Moderate	Mild	% cases with visual field defect
	Whole field loss	Concentric	Crescent				
			Nasal dominant	Temporal dominant			
Left Eye (n = 33)	0	6	7	0	4	7	73
Right Eye (n = 28)	1	3	4	2	5	4	68
Total (n = 61)	1	9	11	2	9	11	70

Among the 27 patients with their both eyes reliably tested, 7 were severely defected.

defect was confirmed by many controlled studies[6-8,10,15,18]. About 17-73% of patients who received VGB therapy was found to sustain visual field defect[6-15]. In Wild et al.[14], a long-term extended cohort project conducted in Japan, 29 (27.6%) of the 102 patients had bilateral visual field defect. The prevalence of bilateral visual field defect in our cross-sectional study was 59% based on 27 patients with both eyes tested. This result is comparable to the foregoing studies in Caucasians[6-13] but is more frequent than that of the Japanese cohort. Although the test procedures, the grading of visual field defect, the patients' age, the duration of epilepsy, and the cumulative dose of VGB were similar between the Japanese cohort and this study, methodological differences do exist. The examination of the visual field in this study was exclusively performed by a well-trained technician on the same static perimetry of Oculus Field Analyzer in a referring center. In the Japanese cohort the examination was performed by several centers conducting open-label extension trial of VGB. The results were reviewed by local personnel and then validated by one of their authors who showed inter-reader variability[14]. In addition, genetic predisposition may also play a role because possibilities of different incidences in different ethnic groups have been proposed by polymorphism study[19].

In this study, we could not find any significant differences in the age, gender, duration of epilepsy, maximum daily VGB dose, and cumulative VGB dose between the groups with and without visual field defect. Although older age[13], male gender[14,15], and larger cumulative doses of VGB[10,17] have been reported to be associated with increased incidence of visual field defect, these are not consistent features. The higher frequency in older age or male gender was not confirmed in this study and another report[12]. Moreover, we found a higher percentage of visual field defects among patients with lower cumulative VGB doses (3575 g) than those reported by Wild et al. (3900 g)[14].

The reason why we separately reported the prevalence of visual field defect in each eye was the difference of the reliability in the two eyes of each individual[11]. The cohort in this study revealed lower prevalence (72.7% of left eye, 67.9% of right eye) of visual field defect than those (88.9% of left eye and 83.3% of right eye) reported by Midelfart et al.[11]. Despite that the age of their patients were older (23-65 years, median 41) than that in ours (21-52 years, median 36), the duration and the cumulative dose of VGB treatment were not different. In their study, Full Field 120 Points Screening test within a range of central fixation to 60˚ was performed. Their figures probably reflect the earlier detection of peripheral defects located between 30˚ and 60˚ eccentrically. In the present study, the most commonly identified visual field loss was crescent and predominantly nasal. In most severely affected patients, concentric constriction or even whole field loss could be observed. Bilateral involvement was frequently found. In Wild et al., nasal field involvement were noted in 25 (86%) of 29 patients with visual field defects, while 17 (55.2%) of 29 had severe bilateral involvement[14]. In 27 of our patients who had both eyes reliably examined, seven (26.9%) have severe defect in both eyes. Unexpectedly, we found five patients with exclusively unilateral involvemet, suggesting variable susceptibility of retina to VGB. We also found more than half of the eyes with mild or moderate defects showed defect in the superior (11/20) and/or nasal (11/20) fields. The selective involvement of superior and nasal visual fields might imply a higher susceptibility to VGB toxicity of the retinal cells at the corresponding areas. Difference in the ocular blood flow may be implicated in the evolution of the damage to the retina based on the finding of ocular blood flow study[20].

Four patients in the present study were found to have vision-related symptoms. We detected asymptomatic visual field defects in patients who had taken VGB for 2.4 months to 4.6 years-consistent with previous reports on silent defects[7-9,11,14]. Furthermore, four of our patients with visual field defects had discontinued VGB for 1.4 to 4.6 years. This may imply a long-term effect of VGB on visual field[12,21], though clinical improvement has been reported[22,23].

The mechanism of VGB-attributable visual field defect has been explored with electrophysiological studies.[7,24,25] The findings in these studies support the abnormality in retina with defects being localized to the inner

and outer retina which are known to be GABAergic[26]. A reduction in ocular perfusion has recently been demonstrated in patients treated with VGB and may have implication in the impairment of visual function associated with the drug[20].

In conclusion, this cross-sectional study confirms the visual field defect associated with VGB therapy and reveals a prevalence rate comparable to the reports based on Caucasian patients. In most cases, the visual field defect is asymptomatic. Although visual field defect might remain stable with continuation of VGB treatment[18,27], it may not be necessarily so. Therefore, the status of visual field and risk/benefit ratio should always be closely monitored when initiating and maintaining VGB therapy.

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