

Retinal Electrophysiological Results in Patients Receiving Lamotrigine Monotherapy

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Summary: *Purpose:* To evaluate the effects on vision in patients receiving lamotrigine (LTG) monotherapy.

Methods: Twenty-four consecutive patients taking LTG for partial seizures were referred for a routine ophthalmologic examination including visual acuity testing, tonometry, slit lamp, and fundus examination. Automated kinetic perimetry, electrooculogram (EOG), and electroretinogram were performed after informed consent was obtained.

Results: In 18 patients finally included, the clinical ophthalmologic examination showed no abnormality. Four patients complained of blurring; among them, one patient had a visual field constriction in both eyes, which, however, was of unclear clinical significance (poor compliance) and a reduced light/dark ratio of

the electrooculogram. One other patient with blurred vision had a reduced EOG, but the visual field was normal. Two patients had a reduced EOG but no visual symptoms. Considering the whole group of patients receiving LTG therapy, the light/dark ratio of the EOG was reduced in a dose-dependent fashion ($p < 0.0001$). The electroretinogram was normal in all patients.

Conclusions: No irreversible visual field impairment in patients treated with LTG was encountered, although a dose-dependent retinal toxicity may have been present. The exact cellular mechanism of the electrophysiologic changes in patients taking LTG remain to be explained. **Key Words:** Lamotrigine—Visual field constriction—Retinal pigment epithelium—Electrooculogram— γ -Aminobutyric acid.

Lamotrigine (LTG) is an antiepileptic drug (AED) effective against both partial and generalized seizures, including generalized absence seizures. Among the documented side effects, visual blurring is reported by 23% of the patients treated with LTG (1). Although it is highly improbable that these visual symptoms are all related to a measurable dysfunction, they have never been precisely evaluated by a complete visual, clinical, and electrophysiologic investigation in patients treated with the drug. One published case exists of visual field constriction in a child treated with LTG and valproate (VPA) (2).

The only established cellular mechanism of LTG is a sodium-current block (3), a mechanism in common with phenytoin (PHT) and carbamazepine (CBZ) (4). However, different from LTG, PHT and CBZ are ineffective against absence seizures and have never been associated with visual field constriction. Therefore it has been advocated that LTG may have as-yet-uncharacterized cellular actions, which could combine with its sodium channel-blocking actions (5). Among other effects, there appears

to be an increase of γ -aminobutyric acid (GABA) levels in the brain (6). Despite the lack of evidence, it can be speculated that if brain GABA levels are elevated by LTG, retinal GABA levels might also be elevated. The extent of any elevation in the retina is unknown.

Tiagabine (TGB) and vigabatrin (VGB) are known to increase GABA levels through inhibition of reuptake and catabolism, respectively (5). The latter, VGB, has been associated with very severe visual dysfunction, including visual field constriction (7) and hypovoltage of the electrooculogram (8) and the electroretinogram (9).

It therefore appeared justified to undertake a clinical and electrophysiologic investigation to state whether a specific effect of LTG on retinal function exists and thus explain visual symptoms occurring in some patients treated with LTG (1).

PATIENTS AND METHODS

Patients

In this cross-sectional observational study, all consecutive patients were diagnosed with partial seizures and were receiving LTG monotherapy (Lamictal) for >6 months. The cohort for the study were recruited retrospectively,

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and the psychophysical and electrophysiologic investigations were undertaken prospectively. The inclusion criteria comprised, in either eye, a visual acuity of ≥ 0.5 , distance refractive error of ≤ 5 dioptres mean sphere and < 2.5 dioptres cylinder, no lenticular changes detected by slit-lamp examination, intraocular pressures (IOPs) of < 22 mm Hg, normal optic nerve head appearances, open angles, no history of congenital color-vision defect, no medication known to affect the visual field, no previous ocular surgery or trauma, no history of diabetes mellitus or treatment with VGB, and no family history of glaucoma.

Methods

After informed written consent was provided, a complete ophthalmologic examination (visual acuity on an EDTRS chart, slit-lamp anterior-segment biomicroscopy, tonometry, and examination of the retina by indirect ophthalmoscopy) was performed in all patients at the Lille University Hospital.

For visual field examination, kinetic perimetry was preferred as it is rapid and more easily performed by epilepsy patients than static procedures, which are more time consuming. In addition, the automated kinetic procedure enables us to determine the area of perception for each isopter, which is more suitable for statistical purposes than the logarithmic parameters provided by automated static perimetry.

A computer assisted kinetic Goldmann-based visual field examination was performed with a commercially available cupola stimulator (Vision Monitor, Pérenchies, France). The radius was 33 cm, and thus the distance between the eye and the cupola was also 33 cm. The back-

ground luminance was 10 cd/m^2 . Four isopters were tested at a speed of $2^\circ/\text{s}$: the peripheral isopter (III 4e Goldmann equivalent) and two midperipheral isopters (III 1a and II 1c, Goldmann equivalent), and one central isopter (I 1e Goldmann equivalent). A near correction was added after the testing of the III 4e isopter. The excentricities of initial stimulus presentation of each isopter were 90, 60, 45, and 30 degrees, respectively. Blind-spot detection (III 4e Goldmann equivalent) was performed at $1^\circ/\text{s}$. No correction glass was used for the peripheral isopter; a correction in accordance with the refractive status was added for the two midperipheral isopters and the central isopter. Patients with fixation loss, false-positive, or false-negative responses of $> 15\%$ were excluded from analysis. Three responses were averaged; each point was tested three times. If a difference of $> 10\%$ was found between the best and the worst response, the procedure was repeated. A perimetric result was accepted only if the variability of each point was $< 10\%$. The right eye was always tested first.

Electrooculography (EOG) measured the variation of the standing potential of the eye between light- (500 candela/m^2) and dark-adapted conditions. In accordance with the standards of International Society for Clinical Electrophysiology of Vision (ISCEV), for each measure, six saccades were averaged to ensure accurate eye-movement performance (10).

Electroretinography (ERG) also was performed in accordance with ISCEV standards (11). The rod response, the maximal response, the oscillatory potentials, the cone response, and the flicker response were subsequently recorded. The amplitude and implicit time of each oscillatory potential was evaluated.

TABLE 1. Clinical and electrophysiologic parameters of patients receiving lamotrigine monotherapy

Patient	Age (yr)	History of previous treatments	Dose LTG (g/day)	Duration LTG (mo)	Cumulative dose (g)	Visual symptoms	Visual field	RE EOG (%)	LE EOG (%)
1	45	Clobazam	500	26	390			150	138
2	22		600	6	108	Blurring	Constriction	133	146
3	16	CBZ, VPA	450	36	486			174	166
4	50	VPA	450	60	810	Blurring		178	181
5	8	Unknown	150	12	54			190	183
6	29		350	12	126			216	197
7	44	CBZ	350	24	252			216	185
8	20	Clobazam	450	60	810			176	190
9	25		450	24	324			186	190
10	29	VPA	400	36	432			192	194
11	38		400	36	432			198	201
12	17		300	36	324	Blurring		223	242
13	34		300	12	108			235	243
14	35	CBZ	200	12	72	Blurring		273	252
15	65		200	28	168			282	268
16	26		100	24	72			291	272
17	29		200	8	48			278	276
18	29		150	24	108			302	285

Four patients complained of blurring, among whom only one had visual field constriction. The light/dark ratio (%) of the right eye (EOG RE) and of the left eye (EOG LE) are presented separately.

CBZ, Carbamazepine; VPA, valproic acid.

The research followed the tenets of the Declaration of Helsinki. The study was approved by the local ethics committee.

Statistics

To evaluate the relation between duration, daily dose, and cumulative dose of LTG with the visual parameters, Spearman's correlation was used rather than regression analysis, as a normal distribution of the LTG dose could not be expected.

RESULTS

Initially, 24 consecutive patients were screened. In total, six patients were excluded: one with an unreliable visual field testing who also refused ERG, one case of oc-

ular hypertension, two patients with homonymous lateral hemianopia, one with an unreliable EOG recording (laser treatment for diabetic retinopathy detected on the fundus examination). Finally, another patient refused to perform ERG.

The analysis was therefore conducted on a base of 18 patients, 10 male and eight female, all receiving LTG monotherapy for >6 months. Clinical details such as age, history of previous treatments, treatment duration with LTG, daily dose, and cumulative dose of LTG are listed in Table 1.

Visual field results

Four patients complained of blurring, but only one patient treated with 600 mg of LTG (Table 1, patient 2) had an overall visual field constriction (Fig. 1), together with an

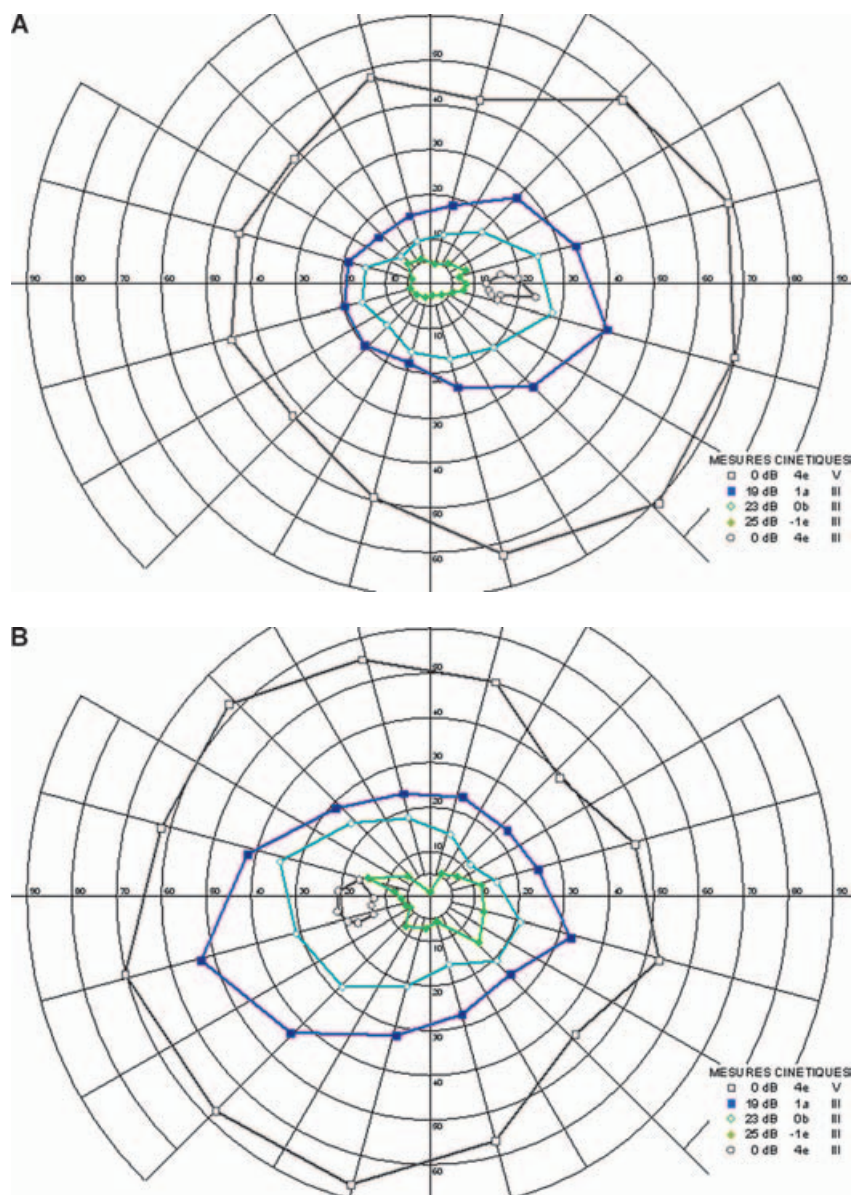


FIG. 1. **A:** Right eye. **B:** Left eye. The visual field of patient 2 with bilateral mild constriction treated with a daily dose of 600 mg, complaining of peripheral blurring.

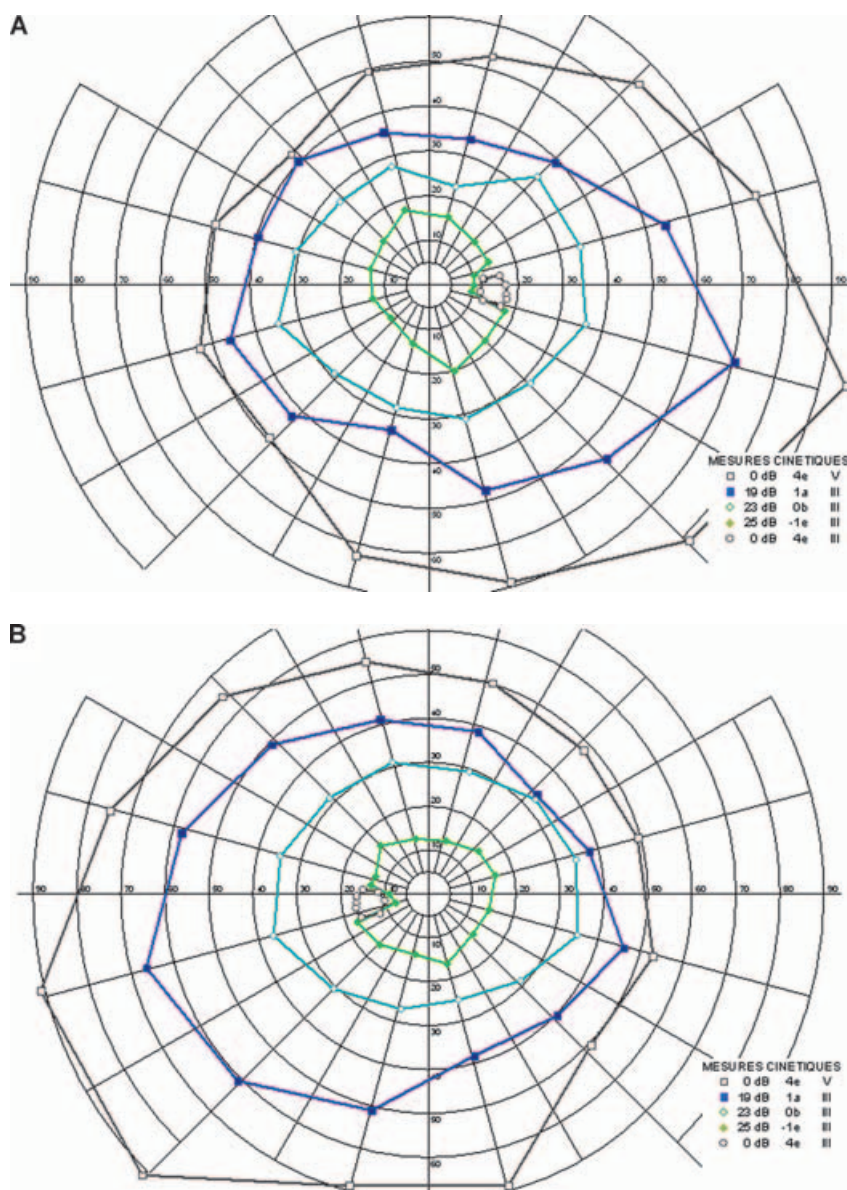


FIG. 2. A: Right eye. B: Left eye. The normalized visual field 1 month after dose reduction of LTG from 600 mg/day to 300 mg/day.

apparent possible localized abnormality superior-nasally and inferior-nasally. The appearance of the blind spot was suggestive of poor patient compliance in the first visual field. The visual field and the EOG were tested 1 month and 6 months after the dose was reduced to 300 mg. The visual field was normalized at 1 month, although this might be due to better compliance (Fig. 2), and the EOG improved (180% in the right eye, 176% in the left eye); after 6 months at 300 mg, the visual field (not shown) and the EOG were stable (185% in the right eye, 189% in the left eye).

No perimetric changes were observed in any other patient with or without visual complaints.

Electrooculography

The light/dark (Arden) ratio was reduced (<180%) in three patients, among them, the patient taking 600 mg

of LTG. In the patient 2, with visual field constriction, the daily intake of the medication was reduced. Interestingly, after dose reduction, as observed with the visual field, the light/dark ratio also improved. For all other patients, the light/dark ratio was in the normal range. However, a highly significant relation (Spearman's correlation coefficient: right eye, -0.97 ; left eye, -0.92 ; both eyes, $p < 0.0001$) could be established in both eyes between the daily dose of LTG at the time of screening and the light/dark ratio of the EOG (Fig. 3). No such correlations were found with the cumulative dose or the duration of treatment.

Electroretinography

The amplitudes of the ERG parameters were all within the normal range (not shown), including patient 2 (see Table 1) with a visual field constriction.

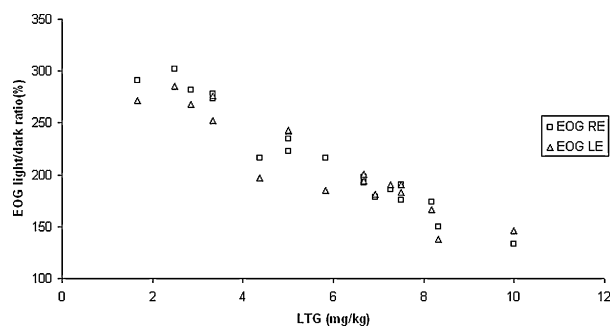


FIG. 3. Electrooculogram (EOG) light/dark ratio (%) of the right eye (EOG RE) and the left eye (EOG LE) plotted against the daily dose of lamotrigine [LTG (mg/kg)].

DISCUSSION

These results confirm the hypothesis of a retinal effect of LTG, documented by EOG recordings, which appears to be dose related. However, at the recommended dose, no adverse effect on visual function could be documented. Only the patient with the highest dose of LTG had a apparent visual field constriction comparable to the perimetric findings characteristic of VGB retinopathy, although these findings could be attributed to poor compliance. Visual field constriction in VGB retinopathy has been associated with two different electrophysiologic abnormalities, EOG (8) and photopic ERG changes (9). In the present case of visual constriction with LTG, only a reduced EOG light/dark ratio but no abnormal ERG recordings were found. In VGB retinopathy, the reduction of the cone flicker response has been found to be correlated with the irreversible visual field impairment (12). The normalization of the visual field after the dose reduction of LTG could thus reflect the fact that no permanent retinal damage was induced, as stated by the normal photopic ERG recording even at the phase of LTG intoxication. Furthermore, as in patients treated with VGB (12), the EOG does not appear to be an indicator of visual impairment in patients treated with LTG, as none of the other patients with a reduced light/dark ratio had a visual field constriction. As with VGB, the reduced EOG could thus indicate a metabolic influence of the drug on the retinal pigment epithelium rather than retinal damage.

However, the underlying mechanism of the changes of the EOG remains to be explained. No direct effect of LTG on the retinal pigment epithelium is known. The cellular action of LTG has been previously investigated and is thought to involve inhibition of voltage-dependent sodium channels (3). However, prolonged LTG treatment also may affect cerebral GABA, among other amino acids, and induce significant elevations in brain GABA compared with baseline (6). Furthermore, if the effect of LTG on retinal levels of GABA is similar to the brain, as it has been demonstrated for VGB (13), then this might explain the electrophysiologic changes observed. The strong correla-

tion between the daily dose of LTG and the light/dark ratio suggests that the EOG might reflect reversible metabolic changes, such as intraretinal GABA levels. An increased intraretinal concentration of GABA could possibly activate transepithelial GABA transport (14) and thus modify the ion flux across the retinal pigment epithelium, reflected by the EOG changes. Recently a potential protective postoperative action of LTG was suggested in rabbits undergoing experimental retinal detachment surgery (15). The cellular effect of LTG treatment was located in the outer retina, which correlates well with the changes of the EOG observed in the present series. However, no changes of the ERG, in particular of the a wave, which would furthermore support the existence of outer retinal changes, were found in the patients treated with LTG.

Although the visual field constriction appeared to be reversible in the patient treated with 600 mg of LTG, its safety regarding the side effects on the visual system must be confirmed by a prospective study with a baseline recording before LTG treatment.

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