Vigabatrin-induced visual dysfunction in Chinese patients with refractory epilepsy

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INTRODUCTION

Vigabatrin is an antiepileptic drug (AED) which irreversibly inhibits gamma aminobutyric acid (GABA)-transaminase, resulting in an increase in brain and retinal presynaptic GABA concentration. It had been approved in Europe and Asia for the treatment of partial and secondarily generalized seizures. Severe symptomatic bilateral visual field constriction was first reported by Eke et al in 1997 in three patients with epilepsy who had received vigabatrin for 2 to 3 years at a dosage of 2-4 g per day (1). These visual defects characteristically start as a bilateral nasal loss, extending in an annulus over the horizontal midline followed by peripheral visual field constriction centripetally in severe cases. Kälviäinen et al had proposed that this retinal toxicity might be genetically determined (2). Initially the incidence of retinal side effects had been estimated to be low, at 0.1%, while subsequent reports suggest the incidence of visual field defects at around 40% and the majority of affected cases are asymptomatic (3-12). The most recent studies point to an incidence of nearly 90% (13, 14). We report the results of ophthalmologic examination...
tion in Chinese patients who were receiving vigabatrin for the management of refractory epilepsy.

METHODS

We identified all patients with epilepsy requiring treatment with vigabatrin from the computerized database of the Prince of Wales Hospital, Hong Kong. We also included a cohort of patients with refractory epilepsy taking other AEDs who had never been exposed to vigabatrin. All patients were followed up at the Neurology Clinic and eye examination was performed as a screening process to determine if any patient had visual defect in view of their exposure to AEDs; this was explained to patients and informed consent obtained. Examinations were performed by a single experienced ophthalmologist (K.K.W.) who was unmasked as to patient anticonvulsant use. Demographic data including the patients’ age, sex, medical and ocular history, the presence of any visual symptoms, details of antiepileptic medical treatment and duration of exposure to vigabatrin, including cumulative and daily doses, were recorded. Each patient received best-corrected visual acuity testing using a projected wall chart, intraocular pressure measurement by non-contact tonometry, slit lamp biomicroscopy, and funduscopy. Conventional automated perimetry with Humphrey Visual Field Analyzer II (Carl Zeiss, Jena, Germany) with a size III white target superimposed on a white background was performed using the Central 30-2 program. Patients who exhibited any substantial loss of reliability such as more than 20% fixation loss were retested. For those with an abnormal visual field test on the first occasion, a follow-up visual field monitoring was arranged. Using the central 30-2 testing strategy, three or more adjacent points on the same side of the horizontal meridian having p value less than 5% on the PD plot, one of which must have p value less than 1%, were regarded as significant visual field loss.

RESULTS

We identified 18 adolescent and adult patients, 8 men and 10 women, with a mean age of 23.8 years (SD 13.4 years), who were taking vigabatrin as add-on treatment for intractable seizures. All patients were able to cooperate with testing. Twelve had symptomatic and six cryptogenic epilepsy. Nineteen control patients with epilepsy were in the control group: 10 men and 9 women, mean age 29.9 years (SD 11.9 years). None of the patients in either group had a history of coexisting optic nerve diseases, ocular trauma, or glaucoma or had undergone ocular operations or laser treatment. No other medications known to be neurotoxic had been prescribed. For patients who were on vigabatrin, the length of treatment with this AED ranged from 13 months to 5 years (mean 24.7 months) and the mean daily dosage was 1581 mg (SD 794 mg). None of the 37 cases had visual complaints and none of their optic cup-disc ratios were greater than 0.4. All vigabatrin users and patients in the control group had corrected visual acuity equal to or better than 20/20. Twenty of 36 (55.6%) eyes of the vigabatrin users showed significant bilateral visual field defects with 80% showing a concentric pattern (Figs. 1 and 2). Funduscopy was normal, as was intraocular pressure, in both groups of patients.
patients. No significant visual field defect was detected in the control group.

DISCUSSION

A number of electrophysiologic abnormalities have been reported in patients on vigabatrin, such as increased b-wave latency and reduced oscillatory potentials on the electroretinogram (2-7, 10). These suggest dysfunction of inner retina cells, including amacrine, ganglion, and bipolar cells; GABA is an inhibitory neurotransmitter in bipolar cells and some amacrine cells and may have a role in modulation of phototransduction from photoreceptors and ganglion cells. Reduced Arden ratio on the electro-oculogram also indicates a reduction in the function of the photoreceptor/retinal pigment epithelium complex (2-7, 10). Pathologic correlation between visual field loss and vigabatrin is available in one patient who developed cardiopulmonary arrest owing to an unrelated condition. Autopsy revealed peripheral retinal atrophy with loss of ganglion cells, atrophic optic papillae, and optic chiasm but relative sparing of macular fibers (15). The loss of peripheral retinal ganglion cells and preservation of macular fibers is consistent with the clinical finding of concentric field loss and relative sparing of central vision. This pattern of field loss is uncommon in the general population. We confirmed a high prevalence of significant visual field constriction induced by vigabatrin in 55.6% of Chinese patients who took this drug and none in other epileptic patients. Since the publication of the high incidence of this potential side effect, the drug had been slowly tapered off from these 18 patients without deterioration in their seizure control. Vigabatrin remains a treatment option for children with infantile spasms (16). In adults the indication is less clear, given also that there are alternative second-line AEDs on the market such as gabapentin, lamotrigine, levetiracetam, pregabalin, and topiramate. In view of the high prevalence of visual field loss and the lack of visual symptoms or visual field abnormalities on confrontation testing, detailed visual field monitoring of patients taking vigabatrin is recommended in patients who cannot be weaned off this drug. However, the frequency or most suitable form of screening is unclear; the Royal College of Ophthalmologists recommends baseline and follow-up assessments every 6 months for a minimum of 3 years (Royal College of Ophthalmologists. The Ocular Side-effects of Vigabatrin (Sabril): information and guidelines for screening 2000. Available at: http://www.rcophth.ac.uk/scientific/publications.html. Accessed March 10, 2006).

Conventionally standard static suprathreshold (Humphrey or Octopus) or Goldmann kinetic perimetry are used to assess visual fields. These techniques require cooperation but many patients with refractory epilepsy on second-line AEDs are infants or young children, or have mental retardation or cognitive impairment, which render measurements unreliable and difficult to reproduce. Measurement of the retinal nerve fibre layer thickness may present an alternative as this is a simple, noninvasive procedure and does not require a high degree of patient cooperation (17, 18). Another potential screening test is rarebit perimetry which appears more sensitive in detecting low degree damage, as conventional perimetry has a limited capacity to reveal early visual loss (19). Whether there is a correlation between the extent of field defects and the duration/daily dose of the drug is uncertain but using this newer technique, visual loss has
been found to be proportional to the accumulated dose (19). It is interesting to note the emergence of another ophthalmologic adverse effect, evident only after years of experience, namely development of angle-closure glaucoma in topiramate users (20, 21). While vigabatrin is no longer prescribed de novo for adult patients, tests for early detection of retinal toxicity are needed as AEDs modify the activity of neurotransmitters such as GABA, glycine, glutamate, serotonin, and acetylcholine, which are found in both brain and retinal tissue.

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REFERENCES
