

The natural history of Vigabatrin associated visual field defects in patients electing to continue their medication

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Abstract

Purpose To determine the natural history of visual field defects in a group of patients known to have Vigabatrin-associated changes who elected to continue the medication because of good seizure control.

Methods All patients taking Vigabatrin alone or in combination with other antiepileptic drugs for at least 5 years (range 5–12 years) were entered into a visual surveillance programme. Patients were followed up at 6-monthly intervals for not less than 18 months (range 18–43 months). In all, 16 patients with unequivocal defects continued the medication. Following already published methodology (*Eye* 2002; 16:567–571) monocular mean radial degrees (MRDs) to the I/4e isopter on Goldmann perimetry was calculated for the right eye at the time of discovery of a visual field defect and again after not less than 18 months follow-up.

Results Mean right eye MRD at presentation was 36.98° (range 22.25–51.0), compared to 38.40° (range 22.5–49.75) after follow-up; $P = 0.338$ unpaired *t*-test. Only one patient demonstrated a deterioration in visual field during the study period and discontinued treatment.

Conclusion Established visual field defects presumed to be due to Vigabatrin therapy did not usually progress in spite of continuing use of the medication. These data give support to the hypothesis that the pathogenesis of Vigabatrin-associated visual field defects may be an idiosyncratic adverse drug reaction rather than dose-dependent toxicity.

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Introduction

In 1989, Vigabatrin (Sabril, Hoechst Marion Roussel/Aventis Ltd) was introduced as a new and effective second-line antiepileptic drug for the treatment of uncontrolled complex partial seizures and infantile spasms.^{1,2} Since 1997 there have been numerous reports of concentric and/or binasal visual field defects associated with the use of Vigabatrin making this the most concerning safety issue with the use of the drug at present.^{3–6} Previous studies have confirmed the high prevalence of visual field defects (up to 30–40%) and the lack of evidence for significant progression or resolution of these defects on cessation of the drug.^{3,7,8} To date, there is little information with regard to the natural history of visual field defects in patients who continue on Vigabatrin.^{3,9} Our study aimed to look at the natural history of visual field defects in a group of patients with known Vigabatrin-associated field loss who opted to continue on the drug because of good seizure control and consequent improvement in quality of life.

Materials and methods

In all, 16 patients who were taking Vigabatrin alone or in combination with other antiepileptic drugs for at least 5 years (range 5–12 years) and who had been noted to have unequivocal Vigabatrin-associated visual field defects were included in the study. Patient ages ranged from 26 to 60 years, average 40 years. All patients had

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opted to continue on Vigabatrin despite documented field loss because of good seizure control. No patient had symptomatic field loss. Each patient was followed up at 6-monthly intervals for not less than 18 months (range 18–43 months) after discovery of the field defect. At each visit patients were asked with regard to subjective visual problems. Best-corrected distance (snellen) and near acuity were recorded. Colour vision was assessed using the 17 number plate version of the Ishihara pseudoisochromatic test. Goldmann kinetic perimetry to the V4e and I4e isopters was performed on the same regularly calibrated machine. Following already published methodology⁷ monocular mean radial degrees (MRDs) to the I4e isopter was calculated for the right eye at the time of discovery of the visual field defect and after a follow-up of not less than 18 months. All patients underwent a slit-lamp examination and direct and indirect dilated fundus examination at each visit.

Results

During the follow-up no patient had any subjective deterioration in visual function. All patients had an initial best-corrected distance acuity of at least 6/9 and N6 for near which did not vary significantly at subsequent visits. All, except one male who was known to be red/green colour blind, managed at least 16 out of the 17 colour plates correctly at each visit. Examination of fundi did not reveal any significant disc or macular abnormalities.

At initial detection of a visual field defect, the mean right eye visual field of the 16 patients was 36.98 MRD (range 22.25–51.0 MRD). Three patients fell into the category of having a severe visual field defect ($VF \leq 30$ MRD). After a minimal follow-up of 18 months, the mean visual field was 38.40 MRD (range 22.5–49.75 MRD). There was no significant change in MRD between the first and final follow-up visits ($P = 0.338$) (Figure 1). Only one patient had a significant deterioration in visual field (≥ 10 MRD) and was advised to discontinue Vigabatrin after 19 months follow-up (Table 1, case 3 and Figures 2 and 3). None of the three patients with severe constriction of visual field showed any further deterioration over at least 22 months follow-up. One of these patients with an initial mean visual field of 22.25 MRD had a final mean visual field of 22.5 MRD after 41 months follow-up (Table 1).

Discussion

Although the exact pathophysiological mechanisms of vigabatrin-associated visual field defects remain unclear the site of toxicity is proposed to be located at the inner retina, where vigabatrin causes irreversible inhibition of

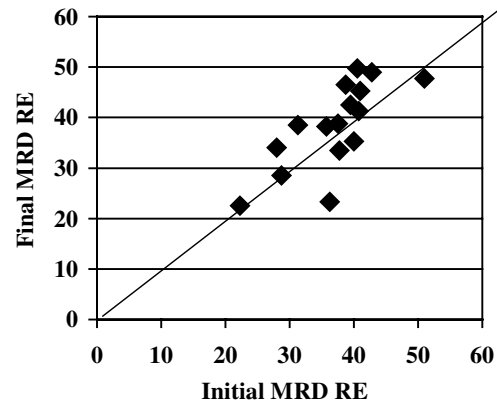


Figure 1 Visual fields in MRD at first recording of a defect plotted against visual field in MRD after a minimum follow-up of 18 months.

GABA aminotransferase with consequent elevation of GABA, a major inhibitory transmitter in the brain and retina.^{10,11} Male preponderance and a lack of relationship between visual loss and cumulative dosage has given rise to the suggestion that an idiosyncratic drug reaction within the neurosensory retina may underlie the pathogenesis of the visual field loss with interindividual susceptibility.⁷ If this was the case, the acquired visual field defect would be expected to remain reasonably stable whether treatment was ceased or not. A recent study by Newman *et al*⁷ showed no evidence of progression or resolution of visual field defects in 21 patients on discontinuing the drug.

Although there have been a few reported cases of improvement in visual field after withdrawal of vigabatrin,^{12–14} other larger studies suggest that field loss is irreversible.^{3,15–17} Several studies have also found no correlation between either treatment duration or cumulative dosage and visual field loss.^{3,7,8} The question as to whether field loss is not only irreversible but progressive with continued use of vigabatrin is less clear. Evidence from this study suggests that visual field defects do not progress significantly or at least appear to plateau with continued use of the drug and do not appear to be dose dependent. Recently, Nousiainen *et al*³ found that after discontinuation of the drug, no significant recovery was observed in visual fields during follow-up, but conversely, no progression was found with continued therapy.

Paul *et al*⁹ showed similar findings in their study. This evidence lends further support to the idea that an idiosyncratic drug reaction may underlie the pathogenesis in some patients. Genetically determined variations in local tissue drug or metabolite deactivation or clearance most probably in the retina are likely to be relevant.⁷ This may have important implications for the quality of life in some patients in whom seizure control

Table 1 (MRDs) field at first assessment and final follow-up

Patient number	Duration of Vigabatrin Tx.(yrs)	Daily dose (g)	Follow-up after VF defect detected (months)	Initial MRD RE	Final MRD RE
1	5	3	18	39.5	42.5
2	8	3	24	37.5	38.75
3	8	1.5	19	36.25	23.25
4	8	1.5	27	41	45.25
5	7	2.5	35	40.75	41.25
6	6	2	35	51	47.75
7	10	4	23	35.75	38.25
8	12	4	35	37.75	33.5
9	7	1	21	40.5	49.75
10	8	1.5	43	40.0	35.25
11	10	3	41	22.25	22.5
12	5	1.5	18	42.75	49
13	10	2	18	38.75	46.5
14	6	3	19	31.25	38.5
15	5	3	22	28	34
16	8	1.5	31	28.75	28.5
Mean of MRD for the 16 eyes				36.98	38.40

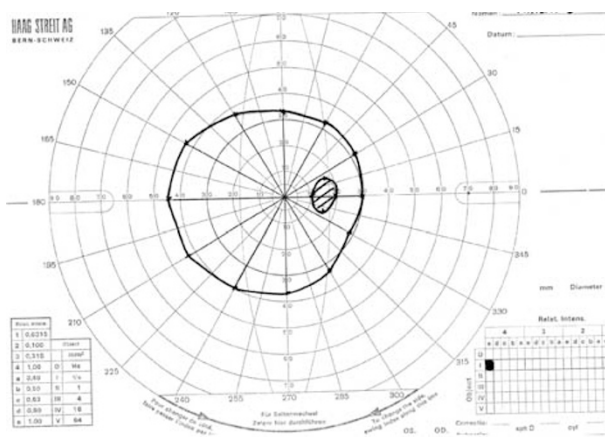


Figure 2 Initial visual field of right eye of patient 3.

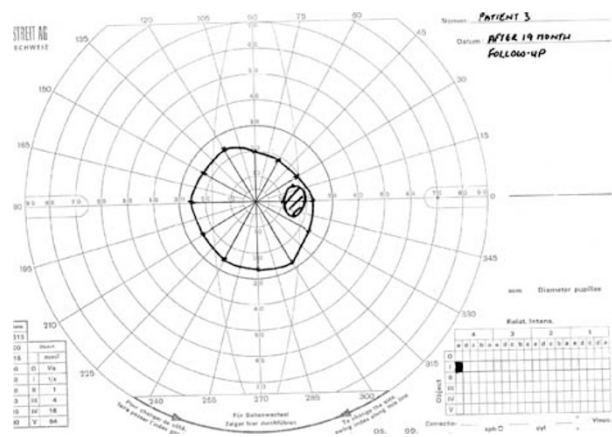


Figure 3 Visual field of right eye of patient 3 after 19 months follow-up.

with other antiepileptic medication has been difficult to achieve. If the risk from uncontrolled seizures outweighed the risk of progressive field loss patients then neurologists might be more confident at opting to

continue vigabatrin. In the meantime patients should continue to be fully informed of the prevalence of visual field defects in vigabatrin users.

References

- 1 Ben-Menachem E. Vigabatrin. *Epilepsia* 1995; **36**: S95–S104.
- 2 Marson AG, Kadir ZA, Hutton JL, Chadwick DW. The new antiepileptic drugs: a systemic review of their efficacy and tolerability. *Epilepsia* 1997; **38**: 859–880.
- 3 Nousianen, Mantyjarvi M, Kalviainen R. No reversion in vigabatrin-associated field defects. *Neurology* 2001; **57**: 1916–1917.
- 4 Wild JM, Martinez C, Reinshagen G, Harding G. Characteristics of a unique visual field defect attributed to vigabatrin. *Epilepsia* 1999; **40**(12): 1784–1794.
- 5 Kalviainen R, Nousiainen I, Mantyjarvi M, Nikoskelainen E, Pastaner J, Pastaner K *et al.* Vigabatrin, a gabaergic antiepileptic drug, causes concentric visual field defects. *Neurology* 1999; **53**: 922–926.
- 6 Lawden MC, Eke T, Degg C, Harding GFA, Wild JM. Visual field defects associated with vigabatrin therapy. *J Neurol Neurosurg Psychiatry* 1999; **67**: 716–722.
- 7 Newman WD, Tocher K, Acheson J. Vigabatrin associated visual field loss: a clinical audit to study prevalence, drug history and effects of drug withdrawal. *Eye* 2002; **16**: 567–571.
- 8 Johnson MA, Krauss GL, Miller NR, Medura M, Paul SR. Visual function loss from vigabatrin: effect of stopping the drug. *Neurology* 2000; **55**: 40–45.
- 9 Krakow K, Polizzi G, Riordan- Eva P, Holder G, MacLeod WN, Fish DR. Recovery of visual field constriction following discontinuation of vigabatrin. *Seizure* 2000; **9**: 287–290.
- 10 Giordano L, Valseriati D, Vignoli A, Morescalchi F, Gandolfo E. Another case of reversibility of visual field defects induced by vigabatrin monotherapy: is young age a favourable factor? *Neurol Sci* 2000; **21**: 185–186.
- 11 Kraemer G, Ried S, Landau K, Harding GFA. Vigabatrin. Reversibility of severe concentric visual field defects after early detection and drug withdrawal: a case report. *Epilepsia* 2000; **41**(Suppl): 144.
- 12 Van Der Torren Kors, Graniewski-Wijnands HS, Polak BCP. Visual field and electrophysiological abnormalities due to vigabatrin. *Documenta Ophthalmologica* 2002; **104**: 181–188.
- 13 Coupland SG, Zackro DH, Leonard BC, Ross TM. Vigabatrin effect on inner retinal function. *Ophthalmology* 2001; **108**: 1493–1496.
- 14 Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314**: 180–181.
- 15 Wilson EA, Brodie MJ, Wong IC, Mawer GE, Sander JWAS, Blackwell N *et al.* Severe persistent visual field constriction associated with vigabatrin (multiple letters). *BMJ* 1997; **314**: 1693–1695.
- 16 Harding HFA, Mackenzie R, Klistorner A. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1998; **316**: 232–233.
- 17 Paul SR, Krauss GL, Miller NR, Medura M, Miller TA, Johnson MA *et al.* Visual function is stable in patients who continue long-term vigabatrin therapy: implications for clinical decision making. *Epilepsia* 2001; **42**: 525–530.