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CORRESPONDENCE

Visual field defects associated with vigabatrin monotherapy in children

In the December issue of this *Journal* Lawden *et al*¹ found in an adult population receiving vigabatrin (VGB), mostly in association with other antiepileptic drugs, a high prevalence (52%) of visual field defects. These abnormalities were not reversible after discontinuation of VGB therapy.

Since 1990, several authors have reported circumferential narrowing of the visual field with characteristic temporal sparing in patients treated with VGB. Although a visual field defect is the most common cause for discontinuation of VGB therapy, no conclusive data are presently available to explain the pathogenesis of this major side effect.^{1,2} Interestingly, retinal dysfunction has been primarily described in patients receiving VGB in combination with other antiepileptic drugs, whereas only a few cases have been reported in patients treated with VGB as a monotherapy.² Despite increasing attention to this complication, the actual prevalence of visual field defect associated with VGB therapy remains poorly defined. Backstrom *et al* have reported a prevalence of less than 0.10%³ and the Hoechst Marion Roussel Pharmaceutical Company has estimated that the incidence of visual field defect is about 0.15%. Other authors, including Lawden *et al*, however, have recently challenged these data, suggesting a considerably higher prevalence.^{1,2} Such discrepancies can be explained by several factors, including delayed appearance of visual field defects after initiation of VGB treatment (several months up to 7 years), high prevalence of non-symptomatic cases,⁴ and lack of systematic studies. In addition, the often used auto-

mated perimetry (Humphrey field analyser) seems to be significantly less sensitive than the Goldmann kinetic perimetry in detecting visual field defects. These limitations are particularly relevant in assessing the incidence of visual field defects in the paediatric population, given the limited compliance during visual field testing and difficulties of diagnosing visual symptoms in very young children.

We have followed up 13 paediatric patients treated with VGB monotherapy, whom we have systematically screened to detect visual field defects associated with this therapy, even in the absence of visual symptoms. Our patients were aged 5 to 16 years (mean 10.5 (SD 3.8) years) and received VGB monotherapy for localisation related epilepsy during an average period of 41 (SD 18) months (range 8-64 months). In all cases, significant improvement of seizure control was obtained. Routine visual field examinations were not performed until the first reports of visual field defects associated with VGB treatment were published.⁵ Since 1997, systematic kinetic perimetry was performed in all patients and careful attention was paid to identify visual symptoms during regular follow up visits. Clinical evidence of impaired peripheral vision was not apparent in any of our patients. However 8/13 (62%) patients were diagnosed with retinal dysfunction characterised by moderate, concentric narrowing of the visual field with temporal sparing in six patients and severe narrowing of the visual field without temporal sparing in two patients; VGB therapy was discontinued in all patients with visual field defects. Partial recovery after discontinuation of the therapy was not found in any of our patients. By contrast with the above results, no evidence of visual field defects was diagnosed with the Goldmann technique, in 12 control patients with localisation related epilepsy treated with carbamazepine monotherapy.

To our knowledge, these data constitute the largest reported series of VGB monotherapy in the paediatric population. Our results show that, despite severe limitations in diagnosing visual field defects in children, systematic screening can reliably detect visual field anomalies in the paediatric population. Routine screening should be performed even in non-symptomatic children. Similarly to recent reports in the adult population,² our data show that visual field defects are not limited to patients receiving VGB in combination with other antiepileptic drugs but can develop also in children on VGB monotherapy. Our series data in a paediatric population are similar to the data reported by Lawden *et al* in an adult population. They also suggest an overall prevalence of visual field defects considerably higher than previously reported, and show that retinal lesions associated with VGB therapy are not reversible.

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Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies

We read with much interest the article by Giovannoni *et al*¹ depicting the clinical entity that goes under the name of "hedonistic homeostatic dysregulation" in parkinsonian patients.

Obviously, the scientific background that allowed the authors to disentangle the syndrome includes two basic concepts: (1) exogenous dopaminergic stimulation and its fluctuations can and do affect mood in the parkinsonian patient and (2) the target of this influence is the reward related dopamine system, arising from the ventral tegmental area of the mesencephalon and innervating wide regions of the frontal and temporal lobes. Nowadays, these concepts may seem trivial, but they were certainly not so in the late 1980s, when I coauthored two papers that appeared in this *Journal*.^{2,3} Contrary to Giovannoni *et al*,¹ I do think it fair to remind readers of these articles, because they may help the interested reader to understand more of the long story of Parkinson's disease, dopamine, and depression. In the 1986 paper,² we provided the first controlled demonstration that a state of dopaminergic hypoactivity (end of dose deterioration) was significantly ($p < 0.05$) associated with a negative mood swing. The control was represented by patients with advanced rheumatoid arthritis whose motor ability fluctuated predictably because of their joint stiffness on awakening. Patients with Parkinson's disease who were steadily depressed (they were depressed even in their mobile periods), were significantly ($p < 0.05$) less prone to a further mood worsening during immobility than patients who did not have a steady depression. We interpreted this as evidence that the dopaminergic system implicated in mood regulation was so severely affected in the former group, to prevent significant fluctuation. But because the motor status of these patients did fluctuate, the system should have been non-nigrostriatal—that is, mesocorticolimbic. These findings, or their essence, were replicated by independent investigators.⁴ In the second paper,³ we used an amphetamine-like compound—methylphenidate—to test the functionality of the reward or pleasure related dopamine system in patients with Parkinson's disease with major depression, in non-depressed patients with Parkinson's disease, in non-Parkinson's disease patients with major depression, and in age matched healthy controls. The methylphenidate test is used by biological psychiatrists, including studies of people addicted to central stimulants, which relates to the thesis of Giovannoni *et al*.¹ The overall result was that patients with Parkinson's disease with major depression showed characteristically a poor euphoriant response to the intravenous injection of the drug. The

pharmacological target of central stimulants is the mesocorticolimbic dopamine system, and particularly the terminals that synapse in the nucleus accumbens, another concept coming back in the paper by Giovannoni *et al.*¹ Hence we suggested that a derangement of this pathway was very likely to have a contributory role in the pathogenesis of depression. Again there was a replication by at least one independent experimenter.⁵

Now, in the work by Giovannoni *et al.*,¹ this earlier evidence not only is indirectly confirmed, but has gained another, more complex clinical significance. Indeed, the picture that they describe includes, apart from mood disturbances, a series of behavioural abnormalities that are akin to those of addicted people. However, the basic concept remains that, as dopamine is the pleasure transmitter and Parkinson's disease is the dopamine disease, one of the multiple Parkinson's disease facets is a disease of the brain pleasure centres.

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Giovannoni and Lees reply:

Cantello further highlights the involvement of the dopaminergic system in mood and reward. His earlier work demonstrates that this system is dysfunctional or hyporesponsive in patients with Parkinson's disease who are depressed. In comparison patients with Parkinson's disease with hedonistic homeostatic dysregulation have cyclical dysfunction of the dopaminergic reward system, with periods of hypofunction and hyperfunction. It is well known and widely accepted that patients with Parkinson's disease have a cyclical mood disorder, which mirrors the fluctuations in their motor function. What we wanted to highlight in our article is that in a few patients this cyclical mood disorder provides the substrate for the development of a behavioural disorder not too dissimilar from addiction. We deliberately avoided using the term addiction because of its negative connotations and the difficulty of untangling the motor requirements from the mood elevating effects of dopamine replacement therapies.

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BOOK REVIEW

Solitary cysticercus granuloma. The disappearing lesion Edited by: VEDANTAM RAJSHEKHAR and MATHEW J CHANDY. (Pp 169, £9.95). 2000. London: Sangam Books. ISBN 0 86311 815 1.

Cysticercosis (*Taenia solium*) is the commonest parasitic disease of the central nervous

system. The infestation is endemic in several countries in Latin America, Asia, and Africa. Epilepsy is by far the most common clinical manifestation and in endemic areas it is the commonest cause of seizures in adults.

This is an excellent monogram with authors who are very experienced in dealing with cysticercosis. The "disappearing lesions" is a term which was introduced from India and the authors go into the aetiology, clinical manifestations, and medical and surgical treatment as well as antiepileptic drug therapy of patients with a single solitary granuloma. The illustrations are excellent and both CT and MRI are well explained and quite clear.

The book is divided into 13 chapters, all the chapters except one are written by authors from the same institute in India. The lack of detailed immunological background to cysticercosis and the possible biological features that can lead to its chronicity, activation, and eventual destruction is a little disappointing. There is one chapter on immunology but it concentrates on the value or lack thereof of immunological tests in the diagnosis of solitary granulomas due to cysticercosis. The chapter on pathology is much more oriented to histopathology rather than the molecular basis of the disease.

The book would have benefited much from including authors from other institutions world wide. Having said that, this book remains valuable as a monogram on a common and in many cases perplexing clinical presentation.

With modern travel, patients with cysticercosis are seen throughout the world; neurologists and neurosurgeons should be familiar with this condition to avoid unnecessary surgery.

This book is not only valuable for those working in endemic areas but perhaps it is more valuable for those working in non-endemic areas of the world where patients present with single enhancing CT lesions and those treating them have little experience of the disease.

RAAD A SHAKIR