Fear can interrupt the continuum of memory

I had always thought that the existence of post-traumatic amnesia, characterised by gaps in the patient’s memory of events after an accident, particularly if the remaining “snapshots” of memory were particularly vivid, meant that the patient must have been knocked out, albeit briefly. I had always rejected the concept that fear, acute anxiety, panic, that which the layman calls “shock”, could be responsible for the phenomena of post-traumatic amnesia. That is until about 6 months ago.

I was driving in the wet, too fast, in a convoy in the outside lane. The conditions were appalling. I was alert. Six or seven cars in front of me were involved in a “front to rear shunt”, precipitated by a car that had been stuck on the inside lane behind a slow moving vehicle, darting without warning into the oncoming traffic. I think that this is what 1 van der Kolk B, Fisler R. Dissociation and the fragmentary nature of traumatic memories; overview and exploratory study. J Traumatic Stress 1995; 8(4): 509–520.

Folates in CSF and age

Low serum and red cell folate concentrations have been reported in up to 42% of elderly healthy subjects in the community or acute geriatric medical admissions, and in 20%–82% of psychogeriatric admissions. 1 Although widely attributed to dietary causes, we have long doubted the causal link between folate deficiency, depression, or dementia. 2,3 Recent community studies have suggested a significant rise in serum total homocysteine and fall in serum folate with age, 4 and there has been renewed interest in a link between Alzheimer’s disease, depression, folate deficiency, and raised serum total homocysteine. 4,5 Other studies suggest that high homocysteine and low folate concentrations are independent risk factors for premature occlusive vascular disease, including cerebrovascular disease. 6

Remarkably, folate in the form of methyl folate is concentrated in CSF by an active transport process at concentrations about three times that in serum. 7 We have had the opportunity to study CSF folate in a group of elderly patients undergoing spinal anaesthesia.

Folate in CSF was measured in 41 patients undergoing surgery at Northwick Park Hospital in a study of spinal anaesthesia and postoperative spinal analgesia by the Department of Anaesthetics. The operations were hip replacement (22), knee replacement (four), hernia (eight), haemorrhoids (three), and varicose veins (four). There were 17 men and 24 women mean age (SD) 74.6 (13.4) years. The patients were otherwise healthy and were not taking medication other than analgesics before surgery.

With informed consent, 2 ml CSF were withdrawn at the relaxing femur position under local anaesthetic before spinal anaesthesia, and was immediately stored at −70°C. Folate in CSF was measured by microbiological assay using a chloramphenicol-resistant strain of E. coli. The figure shows a highly significant decline in CSF folate with age. The mean CSF folate (28 (SD 7.4) μg/ml) between ages 40 and 59 fell 5% between age 60 and 69 (26.6 (SD 8.1) μg/ml). The greatest fall was

Relation of age to CSF folate concentrations in elderly surgical patients.


Anterior superior alveolar neuropathy: an occupational neuropathy of the embouchure

A 31 year old French hornist was referred for evaluation of a 9 month history of pain in her right upper lip.

A member of a major symphonic orchestra, she regularly played 4–6 hours a day. Her symptoms began after a heavy period of playing, with a sensation of excess pressure in the right upper lip. She noticed that brushing her teeth or flossing the teeth overlying a diagram of the lip. She was aware of two other reports of patients similar to ours. Given that the force exerted on the lips by the mouthpiece of a French horn has been measured to exceed 50 N, with displacements of the incisors of up to 18 µm during playing, it is not surprising that these neuropathies occur. French horn and trumpet mouthpieces are significantly smaller than those of the trombone and tuba, and so mouthpiece forces are concentrated onto a very small lip surface area. We suspect that there are other French horn and trumpet players who have experienced similar symptoms to our patient.

Entrapment neuropathy is a potentially reversible cause of disability in brass players, and should be considered in the differential diagnosis of embouchure dysfunction. I thank Drs Jonathan Aviv, and Michael Gelb, for their assistance in caring for the patient.

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3 Lederman RJ, Trumpet player’s neuropathy. JAMA 1987;257:1526.

Clinical and MRI discordance in a case of delayed radiation myelopathy

Delayed radiation myelopathy (DRM) is a rare complication of radiotherapy, especially when the total dose delivered to the spinal cord is less than 50 Gy. From the limited data reported on the radiological features of DRM, typical MRI changes of cord swelling and gadolinium enhancement on T1 weighted images and increased intramedullary signal on T2 weighted images often correlate well with progression of neurological symptoms. We report a case of DRM in which the clinical features remained static at a level corresponding only to the lower end of the normal intramedullary lesion seen on MRI, without radiological evidence of blood–brain barrier breakdown, suggesting that pathological changes due to radiation are not always displayed as visible changes on MRI.

A previously well 71 year old woman presented in December 1997 to the ear, nose and throat department with hoarseness and difficulty swallowing, having discovered a lump in the right side of her neck. Laryngoscopy showed a right pyriform fossa tumour, histologically confirmed as a lymphoepithelioma after biopsy. She was treated with an extensive tumour in the right pyriform sinus and lateral pharyngeal wall with associated lymphadenopathy extending to the thoracic inlet.

Between April and May 1998, she received chemotheraphy comprising 5-fluorouracil and cis-platinum. Radiotherapy was started in June 1998 with fields covering the pyriform sinus and neck, anterior supraclavicular fossa, and posterior neck.

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myelina. However, almost all patients with cervi- cal syringa formation develop marked sensori- motor symptoms or signs in the upper limbs, and a clinical picture of isolated spastic paraparesis is unusual. The main areas of cord damage after radiotherapy would seem to be the lateral corticospinal tracts and posterior columns from radiological-pathological studies. Peripheral ring en- hancement of the cord after gadolinium administra- tion suggests that the major focus of cord damage or at least blood-brain barrier breakdown does not lie within the central cord regions. Consequently, the central cord swelling seen on T2 weighted images may well represent oedema, produced in response to altered vascular permeability after radia- tion damage to the vascular endothelium. In direct intrinsic cord compression, this spindle shaped region of cord oedema has limited correlation with clinical findings, as would be suggested by our case. The presence of gado- linium ring enhancement of the cord, missing in our case, serves as a more reliable marker of structural cord damage, but even in its absence, the diagnosis of DRM can be made in a patient with ascending sensorimotor symptoms within months of radiation therapy, where the only clue to radiation damage to the cord is central cord swelling and vertebral body marrow change with increased signal on T2 weighted images. For- low up MRI shows cord atrophy only in the region of previous gadolinium enhancement, correlating with clinical findings.1 Our case has shown that the ultimate level of disability cannot be judged from the extent of the T2 weighted central cord changes seen on initial MRI.

Due to the inflammatory nature of the pathogenic mechanisms mediating CNS damage during multiple sclerosis, association studies have been focused on candidate genes coding for immunorelevant molecules. The interleukin (IL)-1 gene cluster (including IL-1A, IL-1B, IL-1RN) is located on the long arm of chromosome 2 (2q12–22; OMIM Database of National Center for Biotechnol- ogy Information; www3.ncbi.nlm.nih.gov:80/ Omim) and polymorphic in different sites, represents a good target for association studies in mul- tiple sclerosis. IL-1, in fact, has been detected within multiple sclerosis lesions. Moreover, lipopolysaccharide stimu- lated peripheral blood monocytes of patients with multiple sclerosis produce more, IL-1A and IL-1B than controls.2 Due to the potential involvement of IL-1α and IL-1β in multiple sclerosis, a genetically determined polymorphic variation in their production may contribute to the occurrence of multiple sclerosis, or modulate its clinical features. Furthermore, we have recently reported the association between the variable number of tandem repeat polymorphism (VNTR) of IL-1RN with multiple sclerosis outcome and prognosis.3 IL-1A -889 and IL-1B -511 polymorphic loci are located 375 and 320 kb respectively from IL-1RN VNTR. To determine whether a particular allele or genotype of IL-1A, IL-1B and IL-1RN affects on clinical vari- ables of multiple sclerosis, we performed a case-control association study in a large cohort of patients with multiple sclerosis and age and ethnicity matched healthy controls.

Patients were clinically diagnosed at the multiple sclerosis centre of the San Raffaele Hospital in Milano as affected by clinically definite multiple sclerosis according to Pos- ner’s criteria. All patients had a relapsing- remitting course. Genotype frequencies of the IL-1A -889 polymorphism were calcu- lated in a cohort of 399 patients with sporadic relapsing-remitting multiple sclerosis (247 women, 152 men; age 37.3 (SD 12); mean age at disease onset 27.3 (SD 9.3)) and 439 healthy controls (151 women, 288 men; mean age 37.6 (SD 10.6)). Gene frequencies of the IL-1B -511 polymorphism were calcu- lated in a cohort of 321 patients with sporadic relapsing-remitting multiple sclerosis (203 women, 118 men; mean age 38 (SD 12); mean age at disease onset 27.4 (SD 9.2)) and 403 healthy controls (146 women, 257 men; mean age 38 (SD 10.9)). IL-1A -889 and IL-1B -511 C/T polymorphisms were characterised by polymerase chain reaction (95°C 30 seconds, 55°C 30 seconds, and 72°C 40 seconds; 40 cycles) using genomic DNA and following primers: 5'-GGGCTGAAGTGTCA-TGTTCTC-3' (IL-1A-889 F primer), 5'-GGGT-GCTC-GATGCTATGCTT-G-3' (IL-1A-889 R primer), 5'-GAGCACCCAT-TGATGAGCCTTCCATG-3' (IL-1B-511 F primer), and 5'-TTAA- C3 0 CTT-CCGGATTA-3' (IL-1B-511 R primer). Amplified products were digested with restriction endonuclease (NcoI and Aval).

Statistical analyses were performed with the SAS statistical package (SAS Institute Inc, Cary, NC, USA). The p values were considered not significant (NS) when greater than 0.05. Gene frequencies were compared by χ² test with two degrees of freedom. The homogeneity of Kaplan-Meyer disease free survival curves over strata was tested using the rank-sum Wilcoxon test.

The IL-1A and IL-1B alleles were in Hardy-Weinberg equilibrium in both populations and their distributions were not affected.
IL-1A and IL-1B genotype frequencies in healthy controls (HC) and in patients with multiple sclerosis (MS) as well as in patients with different disease courses (benign and non-benign).

<table>
<thead>
<tr>
<th>Genotype</th>
<th>MS</th>
<th>HC</th>
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</thead>
<tbody>
<tr>
<td>CC</td>
<td>47</td>
<td>18 (189)</td>
</tr>
<tr>
<td>CT</td>
<td>45 (199)</td>
<td>43 (39)</td>
</tr>
<tr>
<td>TT</td>
<td>8 (33)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

Table 1 IL-1A and IL-1B polymorphisms (Table) in multiple sclerosis (MS), the age at disease onset, or the role of inflammatory mechanisms is not as expected and contrast with data coming from multiple sclerosis, these results are somewhat unexpected. We found a similar sex free distribution between patients with multiple sclerosis and healthy controls for both IL-1A and IL-1B polymorphisms (Table). The IL-1A polymorphism (IL-1A: multiple sclerosis vs healthy controls, \( \chi^2 = 0.5, NS \); IL-1B: multiple sclerosis vs healthy controls, \( \chi^2 = 0.4, NS \)).

The possible association between a given IL-1A or IL-1B genotype and accumulation of clinical burden over time was assessed by comparing two groups of patients with multiple sclerosis differing for their disease outcome and classified as “benign” (patients with a stabilised expanded disability status scale (EDSS) score < 3 after at least 10 years from disease onset) and “non-benign” (patients with an EDSS score > 3 after 10 years from disease onset, Table). In the case of the IL-1A polymorphism, the gene frequency of 91 benign was not statistically different from those of the 107 non-benign patients with multiple sclerosis (\( \chi^2 = 0.9, NS \)). As for the IL-1B polymorphism, the gene frequency of the 73 benign patients was also similar to those of the 82 non-benign patients with multiple sclerosis (\( \chi^2 = 0.4, NS \)). To assess whether IL-1A and/or IL-1B genotypes had an influence on the age at onset of multiple sclerosis, Kaplan-Meier disease free survival curves were calculated, plotting the age at disease onset (%) against survival time (Table). We calculated that in those who did not express this cyclin the expression of cyclin B was no different from that in patients who did not express this cyclin. However, the mean concentration of homocysteine in patients who expressed cyclin E was higher than those who did not. To control for the possible influence of other known determinants of serum homocysteine, logistic regression was carried out to see if age, sex, serum creatinine, and serum homocysteine in those patients who expressed the cyclins B or E. The only significant effect was of homocysteine on expression of cyclin E (p < 0.045) which was independent of the other cyclins B or E. The nuclear expression of cyclin E is evidence that the neurons have re-entered the cell division cycle whereas expression of cyclin B indicates progression of the cell to the G2 phase. We suggest that the association of hyperhomocysteinemia with cyclin expression, but not with cyclin B expression, may indicate a mitogenic role for homocysteine. It is possible that the expression of homocysteine in Alzheimer’s disease might be associated with hyperhomocysteinemia. We studied the first 60 patients in the Oxford Project to Investigate Memory and Aging (OPTIMA) where both homocysteine and postmortem hippocampal tissue were available. Forty eight patients had a histopathological diagnosis of pure Alzheimer’s disease, nine had Alzheimer’s disease mixed with vascular pathology and three were unclassifiable without CNS pathology. Total serum homocysteine concentrations were determined in blood samples taken at entry of each patient into the study, on average 29.7 (SD 19) months before death. The expression of cyclins B and C was also assessed by immunohistochemical methods in the nuclei of neurons in the hippocampi by an examiner blind to the diagnosis and to the value of serum homocysteine. As for the cell division markers in neurons in Alzheimer’s disease might be associated with hyperhomocysteinemia.
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Alzheimer’s disease. The incidence of visual field defects was evaluated in 12 control patients with localisation related epilepsy treated with carbamazepine monotherapy.  

To our knowledge, these data constitute the largest report of VGB monotherapy in the paediatric population. Our results show that, despite severe limitations in diagnosing visual field defects in children, systematic screening can 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, 11 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.  


CORRESPONDENCE

Visual field defects associated with vigabatrin monotherapy in children

In the December issue of this Journal Lawden et al 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.  

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.  

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% 1 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. 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, and lack of systematic studies. In addition, the often used automated 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 experience 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 tested for 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. 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 in all patients with VGB related dyschromatopsia.  

To our knowledge, these data constitute the largest report of VGB monotherapy in the paediatric population. Our results show that, despite severe limitations in diagnosing visual field defects in children, systematic screening can detect visual field abnormalities in the paediatric population. Routine screening should be performed even in non-symptomatic children. Similarly to recent reports in the adult population, 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 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 premises: 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 we first published the second paper,5 and appeared in this Journal.6 Contrary to Giovannoni et al,1 we 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,7 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 the inherent daily cyclical focusing and 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 harbour the same condition. 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 in the second paper,8 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 moderate to severe 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.9 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. 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.

Now, in the work by Giovannoni et al., 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 hypersensitive in patients with Parkinson’s disease who are depressed. In comparison patients with Parkinson’s disease with hedonic 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


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 of the world where patients present with single enhancing CT lesions and those treating them have little experience of the disease.

RAAD A SHAKIR