LETTERS

Anticipation in familial amyotrophic lateral sclerosis with SOD1-G93S mutation

A myotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by the degeneration of motor neurons in the spinal cord, brain stem, and motor cortex, resulting in paralysis of limb, bulbar, and respiratory muscles. About 10% of ALS show a familial trait, and up to 20% of familial ALS is caused by missense mutations of Cu/Zn superoxide dismutase (SOD1). More than 70 mutations have been reported, including a mutation hotspot at codon 93.¹ Mice expressing human mutant SOD1 develop age dependent ALS-like neurological symptoms and pathological

features of motor neuron degeneration and cytoplasmic inclusions consisting of mutant SOD1. Patients with SOD1 mutations represent divergent phenotypes, including age of onset, duration of disease, and clinical symptoms, mostly depending on the nature of SOD1 mutation. Acceleration of the age of onset in successive generations called anticipation has been reported in the missense mutations at codon 84 (L84F and L84V) in the SOD1 mutations in Japan, the United States, and Italy.² We experienced anticipation of age at onset in Japanese families with SOD1-G93S mutation. In the families with the G93S mutation, age of onset became younger in the patients of successive generations, exhibiting anticipation (fig 1). We estimated the degree of anticipation of onset age in nine parent-offspring pairs from four Japanese families with G93S mutation of SOD1 (fig 1). The mean age of onset was 64.4 (SD 6.30) years in

the parents, against 44.8 (SD 12.1) years in the offspring in the patients. The mean difference in age of onset in the parent-offspring pairs was 19.6 (SD 10.4) years in the G93S families, showing a statistical significance ($p=0.0005$ by paired t test and $p=0.0077$ by Wilcoxon test; fig 1). Thus, the age of onset accelerated in successive generations in the patients with G93S mutation. In addition, the duration of diseases with G93S mutation was slightly longer in the children than in the parents, although the difference was not significant (fig 1). Six amino acid substitutions (Ser [S], Val [V], Asp [D], Ala [A], Cys [C], and Arg [R]) have been known at glycine 93 of SOD1. Position 93 is located at the apex of a β hairpin joining two β strands of the SOD1 monomer, and it is critical for the stability of the backbone conformation of SOD1. These substitutions are all of the possible single base changes in codon 93, as the changes in the third position of the codon conserve its coding for glycine. However, the age of onset of patients with other mutations at codon 93 such as G93A mutation remained uniform.^{1,3} The patients with G93S mutation present a relatively late onset with a long clinical course, compared with those with G93A mutation: G93S v G93A; 51.9 (SD 14.9) and 43.1 (SD 16.6) years in onset age; and 7.1 (SD 3.1) and 2.4 (SD 1.4) years in disease duration.³ The present results imply that different amino acid substitution at codon 93 resulted in different phenotypes, but anticipation could be a unique feature in familial ALS with G93S mutation. It is still possible that anticipation is due to observer bias in that one does not know whether other offspring are going to get the disease later but are not affected at this stage. Although the mutation testing in all unaffected members is necessary to completely solve this issue, this is somewhat difficult because of ethical problems. At least the eldest sisters in families 1 and 3 (fig 1), who are alive without any symptoms over the age of onset of their parents, are shown to have no mutation of SOD1, further supporting the present view and alleviating the observer bias. Although anticipation has been reported in several neurodegenerative diseases, including most of the polyglutamine diseases, familial amyloidotic polyneuropathy (FAP) with V30M mutation of transthyretin and Creutzfeldt-Jakob disease (CJD) with E200K mutation of prion, the molecular basis for anticipation is understood only in the polyglutamine diseases with instability of CAG repeat expansion.^{4,5} It is unknown whether the mechanism for anticipation is the result of an additional genetic effect or of a related environmental factor. Anticipation was documented in the particular codons of the target proteins in FAP⁴ and CJD⁵, as well as in familial ALS, suggesting the presence of genetic background, which interacts with particular codon mutations. The G93S mutation was reported almost exclusively in Japan, whereas other glycine 93 mutations were demonstrated elsewhere. It would be of interest to compare our results with the G93S mutation in other countries. Factors that generate anticipation of the G93S mutation might be related to the ethnic genetic determinants in addition to the difference of amino acid substitution at position 93, exacerbating the conformational abnormality of mutant SOD1 between successive generations.

E Age differences at disease onset and duration between the parent and offspring generation ($n = 9$, mean (SD, SEM))

Parent age of onset (y)	64.4 (6.30, 2.10)
Offspring age of onset (y)	44.8 (12.1, 4.06)
Paired difference in age of onset	19.6 (10.4, 3.48)
p Value (paired difference in age of onset)	0.0005 [†] /0.0077 [*]
Parent duration of disease (y)	6.55 (1.94, 0.64)
Offspring duration of disease (y)	7.55 (3.61, 1.20)
Paired difference in duration	1.00 (4.55, 1.51)
p Value (paired difference in duration)	0.5287 [†] /0.4008 [*]

Figure 1 Pedigrees and anticipation of familial ALS with SOD1-G93S mutation. The nine parent-offspring pairs in four families (A, B, C, and D) were subjected to statistical analysis. The left and right sided numbers indicate age at onset and years of disease duration. The probands are indicated by arrows. Age differences at disease onset and duration between the parent and offspring generation (E) are calculated for the four families including the family (D) data² (reprinted from *J Neurol Sci* with permission from Elsevier Science), and expressed as mean (SD, SEM). *Paired t test; [†]Wilcoxon test.

K Iwai, M Yamamoto, T Yoshihara, G Sobue

Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Correspondence to: Dr G Sobue, Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan; sobueg@isuru.med.nagoya-u.ac.jp

References

- 1 Radunovic A, Leigh PN. Cu/Zn superoxide dismutase gene mutations in amyotrophic lateral sclerosis: correlation between genotype and clinical features. *J Neurol Neurosurg Psychiatry* 1996;**61**:565-672.
- 2 Ceroni M, Malaspina A, Poloni TE, et al. Clustering of ALS patients in central Italy due to the occurrence of the L84F SOD1 gene mutation. *Neurology* 1999;**53**:1064-71.
- 3 Juneja T, Pericak-Vance MA, Laing NG, Dave S, Siddique T. Prognosis in familial amyotrophic lateral sclerosis: Progression and survival in patients with glu100gly and ala4val mutations in Cu,Zn superoxide dismutase. *Neurology* 1997;**48**:55-7.
- 4 Misu K, Hattori N, Ando Y, Ikeda S, Sobue G. Anticipation in early- but not late-onset familial amyloid polyneuropathy (TTR Met30) in Japan. *Neurology* 2000;**55**:451-2.
- 5 Rosenmann H, Kahana E, Korczyn AD, Kahana I, Chapman J, Gabizon R. Preliminary evidence for anticipation in genetic E200K Creutzfeldt-Jakob disease. *Neurology* 1999;**53**:1328-9.
- 6 Kawata A, Kato S, Hayashi H, et al. Prominent sensory and autonomic disturbances in familial amyotrophic lateral sclerosis with a Gly93Ser mutation in the SOD1 gene. *J Neurol Sci* 1997;**153**:82-5.

Apolipoprotein E4 in the temporal variant of frontotemporal dementia

Although the apolipoprotein E4 (apoE4) allele has consistently been associated with Alzheimer's disease and other types of dementia in many studies,¹ its association with frontotemporal dementia (FTD) is controversial. After our report in 1997 of increased apoE4 allele frequencies in sporadic FTD and its effect on the age at onset,² other studies of cases of FTD with pathological confirmation or tau mutations did not confirm this effect.³⁻⁵ However, recently it has been shown that semantic dementia, the temporal variant of FTD, may be associated with higher frequencies of the apoE4 allele.⁶ Therefore, we have genotyped apoE in our expanded FTD patient population and have assessed whether patients with predominance of temporal atrophy have higher frequencies of the apoE4 allele.

Patients were ascertained through a clinicopathological survey of patients with FTD in The Netherlands.² We identified 111 patients with the diagnosis of probable FTD, established according to the Lund and Manchester criteria. Thirteen of the patients had an autosomal dominant form (defined as at least three affected family members in two generations) of FTD, with tau mutations identified in 10 (P301L, G272V, R406W, and ΔK280), and were excluded from further

analyses. Predominant temporal atrophy, semiquantitatively assessed on CT and/or MRI, was found in 31 (32%) patients, whereas frontal atrophy with or without temporal atrophy was present in 67 (68%) patients. Nine of the 31 patients (29%) with temporal atrophy fulfilled the criteria for semantic dementia, and four patients (13%) showed severe problems in language comprehension, although the diagnosis of semantic dementia could not be definitely established due to incomplete or inconclusive neuropsychological testing. The remaining 18 patients (58%) showed mainly decreased spontaneous speech and word finding difficulties. The clinical diagnosis of FTD was pathologically confirmed in all 17 patients who came to postmortem (five of whom had predominant temporal atrophy). Non-demented control subjects (n=561) were taken from the Rotterdam study.⁷ All patients and controls were genotyped for the apoE allele as described by Slioter *et al.*¹ Both genotype frequencies and apoE4 allele frequencies were calculated for each group and compared with non-demented controls using a χ^2 test.

Six per cent of the 98 patients with sporadic FTD had the apoE4/E4 genotype, compared with 2.3% of non-demented controls ($p=0.04$). This genotype was present in 9.7% of patients with the temporal variant of FTD ($p=0.01$) compared with non-demented controls, compared with only 4.5% in patients with frontotemporal atrophy ($p=0.5$). Genotype frequencies of heterozygote E4 (E4/*) and homozygote E4 (E4/E4) carriers are summarised in table 1. The frequency of the apoE4 allele in all patients with sporadic FTD was 21.9%, compared with 15.3% in the non-demented controls ($p=0.02$). In patients with temporal atrophy the apoE4 allele frequency was as high as 29.0% ($p=0.004$), whereas in the patients with frontotemporal atrophy only 18.7% ($p=0.3$) of alleles was apoE4. No association between ApoE4 and the age at onset, nor the duration of symptoms, was found in the overall group, nor in the subgroups.

Our results show that the apoE4 allele frequency is increased in patients with the temporal variant of FTD compared with non-demented controls. Although a biological hypothesis justifying such an association is still lacking, the effect of the apoE4 allele on the predominance of temporal atrophy compared with frontal atrophy has also been observed in patients with Alzheimer's disease.⁸ To verify the association between the apoE4 allele and the temporal variant of FTD, a large study with pathological confirmation of the clinical diagnosis of FTD is required to exclude admixture of patients with Alzheimer's disease. However, in all 17 patients who were necropsied in our series, including five patients with temporal lobe atrophy, the clinical diagnosis was neuropathologically confirmed. This shows that the clinical criteria according to the Lund and Manchester groups, when combined with neu-

roimaging and psychometric evaluation, are highly accurate. We conclude that the association we previously found between the apoE4 allele and sporadic FTD may be due to a selective increase of this allele in patients with the temporal variant of FTD.

Acknowledgements

We thank Leon Testers for technical assistance. This project was supported in part by grants from The Dutch Brain Foundation, The Internationale Stichting voor Alzheimer Onderzoek (ISAO), the Netherlands Organisation for Scientific Research (NWO), and the Fund for Scientific Research Flanders (FWO)-Belgium.

S M Rosso, J C van Swieten

Department of Neurology, Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands

G Roks, C M van Duijn

Department of Epidemiology and Biostatistics, Erasmus Medical Centre Rotterdam

P Heutink

Department of Clinical Genetics, Erasmus Medical Centre Rotterdam

M Cruts, C van Broeckhoven

Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology (VIB), University of Antwerp (UIA), Antwerp, Belgium

Correspondence to: Dr J C van Swieten, Department of Neurology, University Hospital Rotterdam, Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands; vanswieten@neur.azr.nl

References

- 1 Slioter AJ, Cruts M, Kalmijn S, et al. Risk estimates of dementia by apolipoprotein E genotypes from a population-based incidence study: the Rotterdam Study. *Arch Neurol* 1998;**55**:964-8.
- 2 Stevens M, van Duijn CM, de Knijf P, et al. Apolipoprotein E gene and sporadic frontal lobe dementia. *Neurology* 1997;**48**:1526-9.
- 3 Geschwind D, Karim J, Nelson SF, et al. The apolipoprotein E epsilon4 allele is not a significant risk factor for frontotemporal dementia. *Ann Neurol* 1998;**44**:134-8.
- 4 Pickering-Brown SM, Owen F, Isaacs A, et al. Apolipoprotein E epsilon4 has no effect on age at onset or duration of disease in cases of frontotemporal dementia with Pick- or microvascular-type histology. *Exp Neurol* 1999;**163**:452-6.
- 5 Houlden H, Rizzo P, Stevens M, et al. Apolipoprotein E genotype does not effect the age of onset of dementia in families with defined tau mutations. *Neurosci Lett* 1999;**260**:193-5.
- 6 Anderson C, Fabre SF, Ostberg P, et al. Tau cerebrospinal fluid from semantic dementia patients. *Neurosci Lett* 2000;**294**:155-8.
- 7 Hofman A, Grobbee DE, de Jong PT, et al. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;**7**:403-22.
- 8 Geroldi C, Pihlajamaki M, Laasko MP, et al. ApoE-epsilon4 is associated with less frontal and more medial temporal lobe atrophy in AD. *Neurology* 1999;**53**:1825-32.

Transferrin C2 allele, haemochromatosis gene mutations, and risk for Alzheimer's disease

Alzheimer's disease is a neurodegenerative disease characterised pathologically by the presence of neurofibrillary tangles, senile plaques, and selective loss of neurons. Numerous hypotheses have been suggested for the aetiology and pathogenesis of Alzheimer's disease and one that has gained considerable

Table 1 Frequency of apoE genotypes and E4 alleles in different groups

Group	Patients	Genotype†			Alleles	
		E4/E4	E4/*	No E4	%E4	P-value
Non-demented controls	561	2.3%	26.0%	71.7%	15.3	Reference
Sporadic FTD	98	6.1%	31.6%	62.3%	21.9	0.02
Temporal lobe atrophy	31	9.7%	38.7%	51.6%	29.0	0.004
Frontal lobe atrophy	67	4.5%	28.4%	67.1%	18.7	0.3

†E4/E4, E4 homozygotes; E4/*, E4 heterozygotes; No E4, all other genotypes.

attention is the disruption of the brain iron metabolism in Alzheimer's disease that could lead to an oxidative stress and neuronal damage.¹ An increased iron deposition has been found in the Alzheimer's disease brain, especially in the regions containing more senile plaques and neurofibrillary tangles.^{1,2} Tissue iron can promote oxidative damage through an increase of free radical formation that can lead to subsequent oxidative stress.¹ Among genetic risk factors associated with Alzheimer's disease, the APOE genotype is the major genetic risk factor for sporadic and familial late onset disease. Recently, two genetic risk factors involved in iron metabolism have been associated with an increased risk for Alzheimer's disease. The first one is the allele C2 of the transferrin (Tf) gene, an iron transporting protein detected in senile plaques.^{3,4} In another study⁵ performed on a small group of patients, mutations in the haemochromatosis associated gene (HFE) were overrepresented in Alzheimer's disease compared with controls. We postulated that if these genetic defects in iron metabolism were indeed involved in the pathogenesis of Alzheimer's disease they should be detected in independent populations. Thus, in the present work we investigated whether the C2 allele of the Tf gene or the two common HFE mutations were involved in the pathogenesis or were a disease modifying factor in our Alzheimer's disease population.

We included in this study 108 patients with Alzheimer's disease (80 woman) recruited from both community (n=37) and clinic (n=71) sources. The control sample consisted of 110 unrelated subjects (68 woman) recruited from the community (n=44) and clinic sources (n=66). All control subjects underwent a complete neurological and neuropsychological examination to exclude medical illness and cognitive impairment. All patients were fully evaluated and met the conventional NINCDS-ADRA criteria for probable Alzheimer's disease. After informed consent a blood sample was obtained from patients and controls.

The Tf polymorphism (codon 570) was determined after polymerase chain reaction (PCR) amplification using the mismatched sense primer 5'-GCTGTGCCTT GATGGTACC AGGTAA-3' and antisense primer 5'-GGA CGCA AGCTTCCTTATCT-3' as described.³ Polymorphic exon 15 was amplified from genomic DNA using described conditions.³ The 110 bp product was digested with *Bst*II, separated in a 6% polyacrylamide gel, and stained with silver nitrate. After digestion the C1 allele was converted to a 89 bp fragment while the C2 allele remained 110 bp long. We also genotyped the two common mutations (H63D and C282Y) involved in hereditary haemochromatosis.⁵ APOE genotyping was performed through PCR amplification and *Hha*I restriction enzyme digestion. Allelic and genotypic distributions were analysed by the χ^2 test with the SPSS (version 10.0) statistical package.

Mean age for patients and controls was 78.8 (range 61 to 93) and 73.6 years (range 45 to 92) respectively. Both populations were in Hardy-Weinberg equilibrium for all the polymorphisms. The HFE mutation frequency in the control group was consistent with the frequency of the Spanish population. The frequency distribution of the Tf C2 allele, and C282Y and H63D genotypes among patients with Alzheimer's disease and controls is given in table 1. We did not find associations between Tf C2 allele, H63D, and C282Y mutation frequencies and Alzheimer's disease. Stratification for sex yielded a trend toward

Table 1 Frequencies of the C2 allele of the Tf gene, and C282Y and H63D mutations among AD patients and controls

Genotype	AD patients (% (n))	Controls (% (n))
Tf gene:		
C2 +	31.5 (34)*	35.5 (39)
C2 -	68.5 (74)	64.5 (71)
Allelic frequency		
C1	0.82	0.81
C2	0.17	0.18
H63D +	42.6 (46)†	34.5 (38)
Allelic frequency	0.26	0.20
C282Y +	3.7 (4)‡	3.6 (4)
Allelic frequency	0.02	0.02

*†‡Not significant.
+, one or two alleles.

an increase in the H63D mutation frequency among male patients with Alzheimer's disease (53.6%) compared with male controls (33.3%, $p=0.09$). Stratification for age or APOE status did not yield any significant difference. As expected APOE $\epsilon 4$ was increased in the group of patients (47.2% at least one $\epsilon 4$ allele) compared with controls (11.8%, $p<0.0001$).

In this study we did not find any significant association between the Tf C2 allele or the two common mutations in the HFE gene (H63D and C282Y) and Alzheimer's disease. However, this is by contrast with several studies that have indicated that there is a disruption of brain iron metabolism in Alzheimer's disease.^{1,2} In neuropathological studies iron has been found to be increased in the brain in Alzheimer's disease, especially in regions containing abundant neurofibrillary tangles and senile plaques such as the hippocampus and amygdala.² In particular, selective accumulation of iron has been found within the neurofibrillary tangles and senile plaques in the Alzheimer's disease brain.^{1,2} It is of interest that iron is specifically localised to lesions of Alzheimer's disease and not the glial cells surrounding senile plaques, which contain abundant iron binding proteins.¹ Thus, the accumulation of iron in the Alzheimer's disease brain and the increasing reports implicating oxidative stress, lead us to hypothesise that genetic factors involved in iron metabolism, such as the C2 allele of Tf gene and HFE mutations, could act as a risk factor for the disease. In fact, the C2 allele of the transferrin gene has been associated with an increased risk for Alzheimer's disease in some studies.^{3,4} Furthermore, the two mutations of the HFE gene involved in hereditary haemochromatosis, have also been associated with an increased risk for other diseases, such as dilated cardiomyopathy, myocardial infarction, and type 2 diabetes, which are common complications of iron overload. There is only one study⁷ assessing HFE mutations in Alzheimer's disease. In this study, which was performed in 26 patients with familial Alzheimer's disease, HFE mutations were overrepresented in the group of patients compared with controls.

However, our study is the first assessing HFE mutations in Alzheimer's disease using a large sample. Based on our results neither the C2 allele of the Tf gene nor the HFE mutations were associated with an increased risk for Alzheimer's disease. Thus, the effect of the C2 allele of the Tf gene seems to be lower than previously reported. However, our study can not address the influence of these genetic factors on iron deposition. Resolving this point

deserves further studies evaluating iron quantification in vivo using MRI or at neuropathological examination.

Acknowledgements

This work was supported in part by Generalitat de Catalunya (1999 SGR-00226) to RO and by Fondo de Investigación Sanitario (96/1185) to EB.

A Lleó, R Blesa

Neurology Service, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Hospital Clínic, Barcelona, Spain

C Angelopoulos, P Pastor-Rubio, M Villa, R Oliva

Genetics Service, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Hospital Clínic, Barcelona, Spain

E Buñil

Neurology Service, Hospital General de Vic, Barcelona, Spain

Correspondence to: Dr R Oliva, Genetics Service, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain; roliva@clinic.ub.es

References

- 1 Smith MA, Harris PL, Sayre LM, *et al.* Iron accumulation in Alzheimer disease is a source of redox-generated free radicals. *Proc Natl Acad Sci USA* 1997;**94**:9866-8.
- 2 Good PF, Perl DP, Bierer LM, *et al.* Selective accumulation of aluminum and iron in the neurofibrillary tangles of Alzheimer's disease: a laser microprobe (LAMMA) study. *Ann Neurol* 1992;**31**:286-92.
- 3 Namekata K, Imagawa M, Terashi A, *et al.* Association of transferrin C2 allele with late onset Alzheimer's disease. *Hum Genet* 1997;**101**:126-9.
- 4 van Rensburg SJ, Carstens ME, Potocnik FC, *et al.* Increased frequency of the transferrin C2 subtype in Alzheimer's disease. *Neuroreport* 1993;**4**:1269-71.
- 5 Moalem S, Percy ME, Andrews DF, *et al.* Are hereditary hemochromatosis mutations involved in Alzheimer disease? *Am J Med Genet* 2000;**93**:58-66.

REM sleep behaviour disorder associated with a neurinoma of the left pontocerebellar angle

REM sleep behaviour disorder (RBD) is a type of parasomnia described by Schenck *et al.*^{1,2} It is manifested by vigorous body movements, vocalisation, and sometimes injurious behaviour occurring during vivid and violent dreams. Polysomnographic recordings show abnormal abolition of the generalised muscle atonia that occurs during REM sleep, and concurrent bursts of muscle twitching in the

absence of epileptic activity.¹ There is experimental evidence^{3,4} that the area of the brain stem, and especially the pontine tegmentum, is involved in the pathogenesis of the disorder.⁴ We report a patient who presented with RBD and was diagnosed and treated for a brain stem neurinoma.

The patient is a 59 year old man, an ex-sailor, who was referred to our clinic because of vivid dreams accompanied by violent behaviour during sleep. He described dreams during which he was trying to defend himself while he was threatened by strangers or attacked by animals. Enacting his dreams, he swore at his "enemies," and punched and kicked his bed partner. He had repeatedly injured himself crashing into objects or falling out of bed. This aberrant behaviour had been recurring nightly over a period of six years. One year before the onset of his sleep disturbance, he had noticed impaired hearing on the left, which gradually progressed to almost complete left sided deafness.

On admission, neurological examination was unremarkable except for deafness on the left side. Routine laboratory work up—including a full blood count, electrolytes, immunoglobulins, ANA, ds-DNA, and renal, hepatic, and thyroid tests—was normal. Blood glucose was 7.65 mmol/l and serum VDRL was 2+. Brain stem auditory evoked potentials showed a mild delay of waves III–V on the left compared with the right (2.35 ms and 1.96 ms, respectively). The electroencephalogram, including 24 hour EEG monitoring, was within normal limits. Psychiatric and neuropsychological evaluations did not reveal any major psychopathology. Magnetic resonance imaging (MRI) of the brain revealed a 2.3 cm tumour in the left pontocerebellar angle compatible with a neurinoma (fig 1). Cerebrospinal fluid examination showed four white blood cells, an increased protein of 78 mg/dl (normal range 15–45), FTA-Abs 4+, FTA-Abs IgM negative, IgG 4+, VDRL negative, and TPHA positive in a dilution of 1:640. Because the patient had never been treated for syphilis, which presumably had been latent for an unknown period of time, 30 million units of a penicillin G were given daily intravenously for 10 days. A polysomnogram coupled with videotape recording was performed through the night for eight hours to evaluate the patient's sleep disorder. This showed lack of muscle atonia during most REM periods and bursts of muscle twitching of the arms and legs recorded electromyographically, in the absence of epileptic activity. These polysomnographic findings, along with the videotaped body movements, were considered pathognomonic of RBD.

Figure 1 A neurinoma of the left pontocerebellar angle, 2.3 cm in diameter, shown on magnetic resonance imaging of the brain (T2 weighted image).

The RBD was initially treated symptomatically with 1 mg clonazepam at bedtime. This resulted in a remarkable clinical improvement, beginning on the third day of treatment. About three weeks later, the tumour was surgically removed and the diagnosis of neurinoma was confirmed histologically. Following surgery, RBD manifestations completely disappeared. Subsequently, clonazepam was gradually discontinued over a one month period. At a six month follow up, the patient reported no aberrant behaviour during sleep.

The syndrome of RBD can be idiopathic or it can be a symptom of various neurological diseases. It usually affects middle aged men.² Cases of symptomatic RBD are most often associated with Parkinson's disease, multiple system atrophy, primary dementia, olivopontocerebellar degeneration, and Lewy body dementia.^{2,3} In some of these conditions, RBD may precede other symptoms by years. To our knowledge, there has only been one previous mention of RBD being associated with tumours of the brain stem.² Our patient had a neurinoma of the left pontocerebellar angle which obviously caused his typical RBD episodes by interfering with the brain stem neuronal circuitry. As this circuitry extends bilaterally, the lesion must have affected the pontine region on both sides to cause RBD, perhaps through local oedema.

An unexpected finding in our patient was his latent syphilis, which raised the possibility of an alternative cause for RBD. Syphilis could have affected the brain stem network involved in the pathogenesis of RBD. However, we ruled out this possibility for the following reasons: first, the patient did not present with active infection, as indicated by the relevant serological and CSF findings (negative FTA-Abs

IgM antibodies); second, he did not have any obvious residual clinical signs or symptoms of CNS syphilis; third, his RBD had remained relatively stable over the previous six years; moreover, the development of the tumour obviously preceded the occurrence of the abnormal sleep behaviour by at least a year, as evidenced by the presence of impaired hearing since that time; and finally, the complete remission of RBD following surgical removal of the neurinoma and the absence of any relapse during a six month follow up provides direct evidence for the aetiological association between the two conditions.

In conclusion, RBD may be symptomatic of an underlying brain stem tumour. Thus clinicians should consider the possibility of structural brain stem lesions whenever aberrant behaviour during sleep is present, even in the absence of other prominent neurological signs. A polysomnographic recording in conjunction with brain imaging studies should be performed to investigate the possibility of the coexistence of a brain tumour and RBD. Should that be the case, neurosurgical treatment is clearly indicated.

T Zambelis

Athens University Medical School, Department of Neurology, Eginition Hospital, 74 Vas Sophias Ave, 115 28 Athens, Greece; egslelabath@hol.gr

T Paparrigopoulos, C R Soldatos

Sleep Disorders Clinic, Department of Psychiatry, Athens University Medical School, Eginition Hospital

Correspondence to: Dr Th Zambelis, Athens University Medical School, Department of Neurology, Eginition Hospital, 74 Vas Sophias Ave, 115 28 Athens, Greece

References

- 1 Schenck CH, Bundlie SR, Hinger MG, *et al*. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. *Sleep* 1986;9:293–308.
- 2 Schenck CH, Hurwitz TD, Mahowald MW. REM sleep behavior disorder: an update on a series of 96 patients and a review of the world literature. *J Sleep Res* 1993;2:224–31.
- 3 Jouvet M, Delorme F. Locus coeruleus et sommeil paradoxal. *C R Soc Biol* 1965;159:895–9. [In French.]
- 4 Morrison AR. Mechanisms underlying oneiric behavior released in REM sleep by pontine lesions in cat. *J Sleep Res* 1993;2:4–7.
- 5 Turner RS, D'Amato CJ, Chervin RD, *et al*. The pathology of REM sleep behaviour disorder with comorbid Lewy body dementia. *Neurology* 2000;55:1730–2.

PostScript

CORRESPONDENCE

Mexiletine on segmental hyperhidrosis

Ishibashi *et al*¹ reported the excellent efficacy of mexiletine for the treatment of segmental hyperhidrosis in two patients (who had syringomyelia and cavernous haemangioma of the spinal cord, respectively). They presented the decrement in the patients' sweat rate by oral administration of mexiletine.¹

Previously we performed a clinical study focusing on sweating and identified 10 patients with segmental hyperhidrosis among 30 patients with syringomyelia. We followed up the patients with hyperhidrosis for 1-10 (mean 5.0) years. The amount of sweating did not change in any of them during the follow up period,² although we did not perform a quantitative analysis. Consequently, we speculated that hyperhidrosis persists for at least a year. It is possible that the course of signs in the cases reported by Ishibashi *et al* were modified by the growth or activity of spinal cord lesions. We consider it imperative that these authors describe any spinal cord lesions and how they may have shifted. However, although they did not mention the duration and time courses of the improvement in their patients, we suppose that the duration of the follow up for each patient would not have exceeded several months, judging from how the authors described their experience. In addition, even though they did not test the effects of mexiletine on control subjects or on other parts of the body in the same patients, we can be assured that the improvement in hyperhidrosis was due to the oral administration of mexiletine, on the assumption that the spinal cord tumour could not have changed in such a short time. We consider that it would be informative for clinicians if Ishibashi *et al* were to disclose the drug dosage and the time course of its effects and to describe the features of the spinal cord lesions.

K Sudo, Y Miyazaki, Y Tajima, A Matsumoto

Department of Neurology, Sapporo City General Hospital, Kita 11, Nishi 13, Chuo-Ku, Sapporo, 060-8604 Japan

K Tashiro, F Moriwaka

Department of Neurology, Hokkaido University School of Medicine, Sapporo, 060-8648, Japan

Correspondence to: Dr K Sudo; sudo@med.hokudai.ac.jp

References

- 1 Ishibashi S, Yokota T, Inaba A, *et al*. Mexiletine is effective on segmental hyperhidrosis: report of two cases. *J Neurol Neurosurg Psychiatry* 2002;72:122.
- 2 Sudo K, Fujiki N, Tsuji S, *et al*. Focal (segmental) dyhidrosis in syringomyelia. *J Neurol Neurosurg Psychiatry* 1999;67:106-8.

Authors' reply

We are grateful Sudo *et al*, as they allow us to clarify a point of our study that was not discussed in the paper recently published in this *Journal*.¹ They asked about the possibility of natural remission and the non-specific effect of mexiletine on sweating.

We administered 200 mg/day mexiletine or 400 mg/day carbamazepine to our patients. Both patients noticed their hyperhidrosis was relieved within two days after administration. Although we did not perform a quantitative analysis several months after treatment, the clinical improvement of hyperhidrosis persisted. In addition, the magnetic resonance images of spinal cord lesions (syringomyelia and cavernous haemangioma) in both patients were followed up for two years. During the follow up period, the spinal cord lesions did not change their size, position, and intensity on magnetic resonance imaging. Therefore, the natural course of the spinal cord lesions could not explain the improvement of hyperhidrosis during the treatment and quantitative analysis in our patients.

The sweat rate of the area of observed hyperhidrosis was decreased without a change of the absolute sweat rate on the healthy side after oral administration of mexiletine. We calculated the ratio of the sweat rate on the affected side to that on the healthy side—the ratio was 2.13 before treatment and decreased to 0.97 on day 7 after the treatment. We therefore consider that the mexiletine had an excellent effect only on the area with hyperhidrosis. Although we did not test the effects of mexiletine on control subjects, we think that the result on a healthy area of each patient was an appropriate internal controls for the evaluation of the drug's effect on hyperhidrosis.

S Ishibashi, T Yokota

Department of Neurology and Neurological Science, Graduate School of Medicine, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

Correspondence to: Dr T Yokota; tak-yokota.nuro@tmd.ac.jp

Reference

- 1 Ishibashi S, Yokota T, Shiojiri T, *et al*. Mexiletine is effective on segmental hyperhidrosis: report of two cases. *J Neurol Neurosurg Psychiatry* 2002;72:122.

Patent foramen ovale, cerebrovascular risk, and complement

Nedeltchev *et al*¹ report that the presence of a patent foramen ovale (PFO) is a significant risk factor for recurrent cerebrovascular events, the risk being higher in patients with more than one previous embolic event. They highlight the absence of a current proven medical treatment or prevention regimen. Cardiac right to left shunting is present in a quarter of the population. It is thus worth drawing attention to a particular subgroup of patients with PFO that may be at an even more increased risk than the authors report—sport divers, most of whom fall within the age range of the above study.

Neurological sequelae constitute 80% of decompression sickness. Not only has neuroimaging shown an increased frequency of brain ischaemic lesions in divers, but also multiple such ischaemic lesions have been found specifically in sport divers with PFO.² While PFO patency of haemodynamic significance is a risk factor that necessitates habit modification, often the radiological lesions do

not correspond well to the neurological deficits of experienced divers.

This point, coupled with the increased risk of arterialisation of venous bubbles and the paradoxical nature of bubble genesis, suggest that a PFO is a risk factor in this subgroup for the development of neurovascular disease.³ Unknown is the added risk with age that remains to former divers. A poorly understood mechanism of bubble induced complement involvement in the pathogenesis of the neurological sequelae in decompression sickness has been suggested.⁴ Similarity of such symptoms to the postcoronary bypass syndrome lends support (and hope?) to complement based neuroprotective strategy options for the future.⁵

A K Demetriades

The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK

Correspondence to: Dr A K Demetriades; andreas.demetriades@doctors.org.uk

References

- 1 Nedeltchev K, Arnold M, Wahl A, *et al*. Outcome of patients with cryptogenic stroke and patent foramen ovale. *J Neurol Neurosurg Psychiatry* 2002;72:347-50.
- 2 Knauth M, Ries S, Pohmann S, *et al*. Cohort study of multiple brain lesions in sport divers: role of a patent foramen ovale. *BMJ* 1997;314:701-5.
- 3 Schwerzmann M, Seiler C, Lipp E, *et al*. Relation between directly detected patent foramen ovale and ischemic brain lesions in sport divers. *Ann Intern Med* 2001;134:21-4.
- 4 Ward CA, McCullough D, Fraser WD. Relation between complement activation and susceptibility to decompression sickness. *J Appl Physiol* 1987;62:1160-6.
- 5 D'Ambrosio AL, Pinsky DJ, Connolly ES. The role of the complement cascade in ischemia/reperfusion injury: implications for neuroprotection. *Mol Med* 2001;7:367-82.

Authors' reply

We thank Dr Demetriades for his comments on our study. While the average person with a patent foramen ovale (PFO) may not be at increased risk for neurological events, there seem to be subgroups of patients at increased risk. PFOs with large diameters, right to left shunting at rest, or high membrane mobility and PFOs associated with atrial septal aneurysms have been identified as "dangerous PFOs" by several investigators.¹⁻³ In addition, coagulation abnormalities may promote paradoxical emboli in patients with PFO.⁴ To this list, Dr Demetriades adds special occupations or sports that may be dangerous in people with PFOs, specifically divers. Playing wind instruments has also been mentioned previously.⁵

However, many problems related to PFO remain unresolved. Even in groups that are believed to be at high risk for neurological events, deciding whether and how to treat a PFO cannot be derived from evidence based medicine. Deciding how to proceed depends on the opinion of the attending physician and is not based on data from randomised studies.

The PICSS (PFO in cryptogenic stroke study) showed that secondary prevention of cryptogenic stroke in patients with PFO by using warfarin or aspirin does not result in any difference.⁶ The PC-trial is an ongoing randomised trial we initiated to compare

endovascular PFO closure versus medical treatment alone. We hope that it will provide useful information on secondary stroke prevention in patients with presumed paradoxical embolism. It is also conceivable that divers who have ever had "the bends" would benefit from PFO closure.

Recently reported data suggest links between decompression illness, migraine with aura, and right to left shunts.⁸ These observations not only extend the clinical manifestations of PFO but also bring into discussion new pathophysiological aspects of migraine. If the association between complicated migraine and PFO can be corroborated, a randomised trial on PFO in such patients may be worth while.

K Nedelichev, M Arnold, H Mattle

Department of Neurology, Inselspital, University of Bern, 3010 Bern, Switzerland

S Windecker, A Wahl

Department of Cardiology

Correspondence to: Prof Dr H P Mattle, Department of Neurology, Inselspital, CH-3010 Bern, Switzerland; heinrich.mattle@insel.ch

Reference

- 1 **Schuchlenz HW**, Weihs W, Horner S, *et al*. The association between the diameter of a patent foramen ovale and the risk of embolic cerebrovascular events. *Am J Med* 2000;**109**:456–62.
- 2 **De Castro S**, Carloni D, Fiorelli M, *et al*. Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke* 2000;**31**:2407–13.
- 3 **Mas JL**, Arquizan C, Lamy C, *et al*. Patent Foramen Ovale and Atrial Septal Aneurysm Study Group. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med* 2001;**345**:1740–6.
- 4 **Chaturvedi S**. Coagulation abnormalities in adults with cryptogenic stroke and patent foramen ovale. *J Neurol Sci* 1998;**160**:158–60.
- 5 **Evers S**, Henningsen H, Ringelstein EB. Transient ischemic attacks caused by trumpet playing. *Neurology* 1998;**51**:1709–10.
- 6 **Homma S**, Sacco RL, Di Tullio MR, *et al*. PFO in Cryptogenic Stroke Study (PICSS) Investigators. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in cryptogenic stroke study. *Circulation* 2002;**105**:2625–31.
- 7 **AGA Medical Corporation**. PC-trial: patent foramen ovale and cryptogenic stroke. 18 January 2002. <http://www.amplatzer.com/physicians/pfo/pctrtrial/>.
- 8 **Wilmshurst P**, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. *Clin Sci (Lond)* 2001;**100**:215–20.

Demyelination in the brain as a paraneoplastic disorder: candidates include some cases of seminoma and central nervous system lymphoma

We read with interest the report of Ayuso-Peralta *et al*,¹ which describes a 58 year old woman who presented with several neurological symptoms. Brain imaging was consistent with leukoencephalopathy, and analysis of blood and cerebral spinal fluid was unrevealing. A few months later the patient experienced further neurological deterioration and an open brain biopsy showed central nervous system (CNS) lymphoma, together with diffuse demyelination.

The authors observed that the presentation of cerebral lymphoma as a diffuse leukoencephalopathy is not frequent and they discuss

possible aetiologies of the predominant demyelination in their case. They do not mention the possibility of a paraneoplastic aetiology.

The authors reference a similar case² previously reported in the *Journal*. That report also does not acknowledge a possible paraneoplastic aetiology for prominent diffuse brain demyelination preceding the discovery of CNS lymphoma. Two other recent reports in the *Journal*^{3–4} described focal tumour-like lesions of brain demyelination that preceded the discovery of CNS lymphoma. Only one of these reports⁴ mentioned laboratory data that suggested consideration of a paraneoplastic aetiology, the presence of serum antibodies directed against myelin oligodendrocyte glycoprotein.

One report elsewhere⁵ has described a patient who had a non-neurological malignancy and seminoma and who subsequently developed a paraneoplastic syndrome simulating encephalitis associated at autopsy with multiple foci of demyelination confined to cerebral white matter. Two other reports elsewhere^{6–7} have described biopsy confirmation of large focal demyelinating lesions in the brain associated with seminoma. The authors of these three reports all strongly considered the possibility of a paraneoplastic aetiology for the brain demyelination associated with seminoma, probably because the temporal association was close and the spatial association was distant.

The associations between brain demyelination and CNS lymphoma have been close, both temporally and spatially, making considerations of aetiology more complex. Taken together, the seminoma reports and the CNS lymphoma reports have many similarities in their patterns of associated brain demyelination, raising the possibility of similar mechanisms of demyelination. Many questions concerning aetiology remain unanswered. Given the information available, we suspect a paraneoplastic aetiology in all of these cases. We feel that future reports of brain demyelination associated with CNS lymphoma should consider this possibility in their data collection and in their discussion of results.

J H Jaster

Delta Medical Center, 1905 Harbert Avenue, Memphis, Tennessee 38104, USA

F C Dohan Jr

Division of Neuropathology, Department of Pathology, University of Tennessee, Memphis, Memphis, Tennessee 38163, USA

T F O'Brien

Department of Pathology, Methodist University Hospital, 1265 Union Avenue, Memphis, Tennessee 38104, USA

Correspondence to: Dr J H Jaster, Department of Medicine, University of Tennessee, 1905 Harbert Avenue, Memphis, Tennessee 38104, USA; harbert38104@yahoo.com

References

- 1 **Ayuso-Peralta L**, Orti-Pareja M, Zurdo-Hernandez M, *et al*. Cerebral lymphoma presenting as a leukoencephalopathy. *J Neurol Neurosurg Psychiatry* 2001;**71**:243–6.
- 2 **Brecher K**, Hochberg FH, Louis DN, *et al*. Case report of unusual leukoencephalopathy preceding primary CNS lymphoma. *J Neurol Neurosurg Psychiatry* 1998;**65**:917–20.
- 3 **Alderson L**, Fetell MR, Sisti M, *et al*. Sentinel lesions of primary CNS lymphoma. *J Neurol Neurosurg Psychiatry* 1996;**60**:102–5.
- 4 **Kuhlmann T**, Schroter A, Dechent P, *et al*. Diagnosis of a multifocal B cell lymphoma with preceding demyelinating central nervous system lesions by single voxel proton MR spectroscopy. *J Neurol Neurosurg Psychiatry* 2001;**70**:259–62.

5 **Kaluza J**, Slowinski J, Bujny T, *et al*.

Paraneoplastic syndrome simulating encephalitis in the course of testicular seminoma. *Folia Neuropathol* 1997;**35**:24–8.

6 **Wong K**, Poon P, Berry K, *et al*.

Paraneoplastic demyelinating disorder in the brain of a patient with seminoma. *J Comput Assist Tomogr* 1998;**22**:136–8.

7 **Jaster JH**, Bertorini TE, Dohan FC, *et al*.

Solitary focal demyelination in the brain as a paraneoplastic disorder. *Med Pediatr Oncol* 1996;**26**:111–5.

Genotype predisposition to leukoaraiosis

Leukoaraiosis, which can cause symptoms ranging from a mild cognitive impairment to severe subcortical dementia,¹ is a significant public health problem. One quarter of subjects aged 65 years or over are affected by some degree of white matter changes.² Ischaemic demyelination and small vessel disease seem to be important features of the underlying pathological process of this entity.^{1,2} Age, hypertension, and a previous stroke event have been proved to be the main clinical risk factors.^{1,2} A number of genetic susceptibility factors for leukoaraiosis have been put forward, with the assumption of polygenic aetiological factors. We were pleased to read the article by Hassan *et al* in this journal.³ The authors stated that the angiotensin converting enzyme insertion/deletion (ACE I/D) polymorphism D/D genotype was a significant independent predictor for leukoaraiosis in patients presenting with classic lacunar syndromes.³ We earlier conducted large prospective studies in which we also examined the importance of the ACE D allele and other common mutations in the development of small vessel infarction and leukoaraiosis.^{4,5} Our results were consistent with the findings of Hassan *et al* and support their results from several other aspects. (1) Our stroke study confirmed the genetic heterogeneity of ischaemic stroke in that the ACE D/D genotype proved a significant susceptibility genotype for small vessel brain infarction, as did the Leiden V mutation for large brain infarction.⁴ (2) In our leukoaraiosis study, the ACE D/D genotype was found to be a significant risk factor for leukoaraiosis in combination with brain infarction.⁵ (3) We also reported that clustering of the homozygous MTHFR 677TT and ACE D/D mutations in one person can mean a moderate (about fivefold risk), but highly significant ($p < 0.0005$) risk of leukoaraiosis without infarction.⁵ These data from different approaches reconfirm the possible aetiological role of the ACE D/D genotype in leukoaraiosis relating to small vessel brain disease. The genotype differences may explain why some patients who are exposed to clinical risk factors such as hypertension, exhibit a much higher susceptibility to leukoaraiosis than other subjects with the same clinical risk factors. Besides the classic clinical risk factors, the consistently growing knowledge of the genetic background of leukoaraiosis may permit the recognition of a large population at high risk of a new type of white matter damage, and hence this may lead to a more effective prevention.

Z Szolnoki, M Szabó

Department of Neurology and Neurophysiology, Pándy Kálmán County Hospital, Gyula, Hungary

F Somogyvári

Central Laboratory, Pándy Kálmán County Hospital

Correspondence to: Dr Z Szolnoki, H-5600 Békéscaba, Pipacs köz 9, Hungary; szolnoki99@hotmail.com

References

- 1 **Pantoni L**, Garcia JH. Pathogenesis of leukoaraiosis, a review. *Stroke* 1997;**28**:652–9.

- 2 van Gijn J. Leukoaraiosis and vascular dementia. *Neurology* 1998;51:3-8.
- 3 Hassan A, Lansbury A, Catto AJ, et al. Angiotensin converting enzyme insertion/deletion genotype is associated with leukoaraiosis in lacunar syndromes. *J Neurol Neurosurg Psychiatry* 2002;72:343-6.
- 4 Szolnoki Z, Somogyvári F, Kondacs A, et al. Evaluation of the roles of the Leiden V mutation and ACE I/D polymorphism in subtypes of ischaemic stroke. *J Neurol* 2001;248:756-61.
- 5 Szolnoki Z, Somogyvári F, Kondacs A, et al. Evaluation of the roles of common genetic mutations in leukoaraiosis. *Acta Neurol Scand* 2001;104:281-7.

BOOK REVIEWS

Neurochemistry of consciousness: neurotransmitters in mind

Edited by Elaine Perry, Heather Ashton, and Allan Young (Pp 346, EUR65.00). Published by John Benjamins Publishing Company, Amsterdam, 2002. ISBN 90-272-5156-8

Consciousness is a portmanteau word, full of rich and different meanings: contrast Marxian, Freudian, and anaesthesiologists' use of the term. In recent years it has also become a fashionable hunting ground for neuroscientists, who are rarely troubled by such complexities. For them, consciousness is being awake rather than asleep, being reducible to awareness. Sweeping aside centuries of philosophical debate, they ponder over whether "it" "resides" in specific anatomical brain structures, in microtubules, in patterns of neurotransmitter release, or whatever. The present book is typical of this type of cheerfully unsophisticated empiricism: its hunt for what the editors call "NCCs"—neural correlates of consciousness—focuses on neurotransmitters, hence the subtitle. However, the concern with "mind" ceases at that point; this elusive phenomenon finds no place in the book's index. The central question for the editors seems to be whether the acetylcholine or the dopaminergic system is the more likely substrate for conscious awareness. This reductionism characterises most of the chapters. That on memory, for instance, abandons even animal memory for a discussion of a physiological phenomenon called long term potentiation, and even the psychoanalyst Mark Solms, on dreams, who surely ought to have a broader perspective, confines himself to contrasting cholinergic and dopaminergic hypotheses. However, the authors are clearly writing to an editorial brief: each chapter, in a book ranging from discussions of attention and motivation through psychotropic drug mechanisms to mental retardation and autism, following a brief nod to marginally wider concerns, offers a neurotransmitter by neurotransmitter list of potential associations or correlations with "states of awareness." Within these limitations many of the chapters provide competent student friendly overviews of their themes. If the book's pretensions weren't so much larger this would be fine; as it is, those hoping for a more multilevel or theoretically informed discussion will be disappointed.

Steven Rose

Risk control and quality management in neurosurgery

Edited by H-J Steiger and E Uhl (Pp 227, EUR108.000). Published by Springer Verlag Wien, Wien, 2001. ISBN 3-211-83678-0

This is an interesting and timely publication. The book contains a compilation of material presented at an international meeting held in October 2002. It has been divided into various sections that take the reader through grouped papers and topics and finally a projection into the future. As would be expected, the material covers experience and lessons gained in other areas such as aviation and nuclear research. The authors, generally senior in status, originate from Europe, the United States, and the United Kingdom and therefore offer a diverse collection of views, opinions, and experience relevant to a very wide readership. The increasing requirements for quality assessment and competency make this a very valuable reference book for both departmental and institutional libraries. However, it certainly will be of value to individual readers. It should be recommended reading for trainees to understand the principles and the ongoing thought behind many of the practices and control measures that they will encounter and will need to participate in as their experience and seniority advance. The quality of contributions and the outline of the information do vary, as would be expected in such a compilation, but overall very few pages or chapters do not prove insightful nor provide useful information and guidelines. It will be of value to all medical disciplines, since the principles are universal and the terms of reference or yardsticks used are convertible or transferable. It is highly recommended.

J Van Dellen

Primary progressive multiple sclerosis

Edited by M Filippi and G Comi (Pp 128, EUR47.95). Published by Springer, Milan, 2002. ISBN 88-470-0167-6

The field of multiple sclerosis (MS) is awash with literature on every aspect of the disease ranging from epidemiology and genetics to pathology and treatments. It is unusual, therefore, to find a lacuna in this niche but this book seems to have found one.

Primary progressive multiple sclerosis is written to encapsulate the latest evidence on aspects of this condition, which until recently was not regarded as important in understanding demyelinating disease. Filippi and Comi have brought together all the important players in the study of primary progressive MS. Their contributions summarise the latest information on the epidemiology, genetics, immunology, pathology, imaging, and clinical trials and therapies in primary progressive MS. This book is meant to be a useful guide to the subject and does not profess to be an authoritative account. However, it occasionally is a little too brief in its explanations and definitely lacks pictures, tables, and diagrams in the early part of the book. This makes it a rather bland and dry account initially. When the diagrams and scanned images do appear in the latter parts of the book, many of them lack definition and it is not always easy to see the details that are being referred to.

All in all this is a good up to date summary of the latest news in primary progressive MS and in particular the imaging aspects of the disease, as would be expected from the interests of the editors. It would be a useful adjunct to other literature for those working in the field of demyelinating disease.

Omar Malik

Multiple sclerosis: a guide for the newly diagnosed, 2nd edn

By N J Holland, T J Murray, and S C Reingold (Pp 160, US\$21.95). Published by Demos Medical Publishing Inc, New York, 2002. ISBN 1-888799-60-9

This book is an invaluable guide for patients with multiple sclerosis (MS), as well as their friends and families. The fact that a second edition has become necessary is extremely encouraging for those involved with MS and highlights the recent therapeutic advances for this still devastating diagnosis. Most people who develop MS are desperate for information about their new disease and many turn to the internet to find this. Unfortunately, they are then faced with misleading or simply incorrect information, which can leave patients confused or disillusioned.

The authors present detailed information in the first two chapters covering the pathological processes causing the symptoms of MS and the diagnostic tests in use. Uncertainties in both these fields are explained. The next two chapters deal with treatments, including conventional and alternative or complementary therapies; the text is clear about the lack of a cure for MS but discusses all the options including steroids for acute attacks, disease modifying drugs, and symptomatic treatments. There is a whole chapter on the important issues of lifestyle—diet, rest, sexual function, pregnancy, etc.—that help patients to control their condition. A further chapter concentrates on the psychological impact of a diagnosis of MS and its effect on relationships. Employment issues are deservedly dealt with on their own, with practical advice on when and how to disclose the diagnosis and the legal implications of disclosure both at work and on application forms such as those for health and life insurance.

The latter part of the book deals with clinical and research trials in MS that will help patients to understand how trials are designed and why treatments are offered to patients with specific disease types. The many fields in which MS research is ongoing are described and the questions being asked by investigators are well presented.

The book ends with more practical advice on how to get further information about specific topics; however, this is predominantly aimed at the North American readership with emphasis on the MS societies of the United States and Canada.

In summary, this is an excellent book, which presents all the facts in a straightforward but sympathetic way. As well as the medical facts about the disease, it is full of practical advice covering all life topics, areas that are often neglected by busy physicians. It is highly recommended to all those whose lives have been affected by this disease.

Valerie Stevenson

Disordered mind and brain: the neural basis of mental symptoms

By Peter F Liddle (Pp 320, £40.00). Published by Gaskell, London, 2001. ISBN 1-901242-65-X

The premise of this book is that the key to understanding the neural basis of the major mental disorders is an understanding of the origin of five symptom clusters or dimensions common to these disorders. These are reality distortion (hallucinations and delusions); disorganisation (of thought and behaviour); psychomotor poverty and excitation; depression and elation; and anxiety. Thus, there are five chapters each devoted to a description of a specific dimension and an exposition of how it is correlated with cognitive abnormalities derived from the dysfunction of specific neural processes.

These central chapters are preceded by five chapters describing the neuroscience of brain systems thought to be involved in generating the various symptom clusters. These are brief and the literature reviews are in no way comprehensive. Nevertheless, they serve the purpose of informing the reader of the basic neuroanatomical and neurophysiological concepts that underpin Professor Liddle's approach to understanding mental illness.

The final four chapters summarise the current evidence regarding the neurobiology of schizophrenia, bipolar affective disorder, obsessive compulsive disorder, and psychopathy.

Each ends with a synthesis that integrates this with the previous account of how the symptom clusters arise.

The explanatory power of Professor Liddle's thesis concerning the neural basis of mental symptoms is stronger for some symptom dimensions, such as reality distortion, than others, such as distortion. But it is the general unifying approach that is the major strength of this book—the detail will certainly be honed over the next decade. Another strength is that this is a self contained book! It assumes no neuroscientific or medical knowledge other than the most basic. There are many excellent colour illustrations. Therefore, this book can be highly recommended to anybody interested in the disordered mind and brain.

Eileen Joyce

CORRECTIONS

Rosso SM, van Swieten JC, Roks G, *et al.* Apolipoprotein E4 in the temporal variant of frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2002;**72**:820.

Due to the style used in house for listing authors affiliations in the Letters section of the journal, the author's names have been incorrectly listed. The correct order should read as follows:

Rosso SM, Roks G, Cruts M, van Broeckhoven C, Heutink P, van Duijn CM, van Swieten JC

This also applies to:

Lünemann JD, Kassim N, Zschenderlein R, *et al.* Rhabdomyolysis during interferon- β 1a treatment. *J Neurol Neurosurg Psychiatry* 2002;**72**:274.

The correct order of the authors is: Lünemann JD, Schwarzenberger B, Kassim N, Zschenderlein R, Zipp F.

Aarsland D *et al.* Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study. *J Neurol Neurosurg Psychiatry* 2002;**72**:708–12. An error occurred in the production process in which the codes of the two lines were erroneously interchanged. The correct figure appears below:

Figure 2 Change in mini mental state examination (MMSE) score from baseline over the two treatment sequences. Values are mean (SE).