The possibility that large segments of PS1 were spliced out was also examined. RNA extracted from the blood was reverse transcribed and PCR was performed to produce cDNA from exon 3 to exon 12 of PS1 (sense primer: 5’-GTTACC TGCACCGTTGTCCTACT -3’, antisense primer: 5’-GTTACC TGCACCGTTGTCCTACT -3’, antisense primer: 5’-GGAGATTGGAAGAGCTGGC TGCACCGTTGTCCTACT -3’, sense primer: 5’-GTTACC TGCACCGTTGTCCTACT -3’). The novel mutation Phe237Ile in PS1 was confirmed by restriction fragment length polymorphism. The PCR product was digested with Hph I (Biolabs) and was resolved in 1.5% agarose gel. A normal allele was characterised by the single fragment of 369 bp and a mutated allele by two fragments of 248 and 121 bp. We also searched for this mutation in 197 Japanese patients from a necropsy series at a geriatric hospital in Tokyo (73 non-demented controls without CNS disorder, 59 sporadic patients with Alzheimer’s disease, and 65 disease controls with various CNS disorders). The possibility that large segments of PS1 were spliced out was also examined. RNA extracted from the blood was reverse transcribed and PCR was performed to produce cDNA from exon 3 to exon 12 of PS1 (sense primer: 5’-GTTACC TGCACCGTTGTCCTACT-3’, antisense primer: 5’-GGAGATTGGAAGAGCTGGCAATG-3’). The PCR product was analyzed...
in 1.5% agarose gel. The apolipoprotein E gene (ApoE) was also genotyped as described previously. All analyses were confirmed by a repeat procedure. The remainder of the patient’s family members did not consent to genetic examination.

Sequence analysis of PS1 disclosed a novel heterozygous T to A transition at the first position of codon 237 (fig 1). This mutation is predicted to result in the substitution of a phenylalanine for isoleucine (Phe237Ile). Restriction analysis confirmed the presence of a heterozygous mutation of Phe237Ile. There was no additional mutation in the whole coding exons of PS1 and PRNP, exon 16 and 17 of APP, or splice acceptor site of intron 11 of PS1. This mutation was not found in 197 patients from the necropsy series. There was no deletion of the large segment of PS1 cDNA including exon 9, which was previously reported in familial Alzheimer’s disease with spastic paraparesis. The ApoE genotype of our patient was 3/3.

As there is no similar disease in his family and DNA samples from the remainder of the family members were not available, we cannot rule out the possibility that the Alzheimer’s disease was due to genetic abnormality and development of the disease. However, we suppose that the PS1 Phe237Ile mutation is responsible for pathogenesis of our patient’s disease.

Any possibility that the similarity to the P301L mutation of PS1 is the most popular genetic cause of familial Alzheimer’s disease (FAD) and all mutations except Glu318Gly are responsible for early onset Alzheimer’s disease. Glu318Gly is a frequent polymorphism which is found in 3.3% of the general population. To exclude the possibility that Phe237Ile is a polymorphism in a Japanese population, we screened for the presence of Phe237Ile in 197 patients from a necropsy series including non-demented controls and patients with sporadic Alzheimer’s disease. The same mutation was not found in this population, suggesting that Phe237Ile is a rare mutation associated with FAD.

Secondly, two mutations in the transmembrane V domain produce very early onset Alzheimer’s disease. The patients with Leu235Pro developed Alzheimer’s disease at 72.1 (SD 5.9) years, duration of disease of 7.3 (SD 1.5) years, and MMSE score of 23.5 (SD 4.7). The control group consisted of 19 subjects, mean age 71.2 (SD 7.3) years, without symptoms or signs of brain disorders, all with MMSE scores above 28.

The ethics committees at the universities of Umeå and Göteborg approved the study, conducted in accordance with the provisions of the Helsinki Declaration.

Analyses of CSF were performed using enzyme linked immunosorbent assays (ELISA) as described previously in detail for total tau, Aβ42, NFT, GAFP, and S-100β. The NSE in CSF was determined using a commercial ELISA from AB Sangtec Medical, Bromma, Sweden.

The Mann-Whitney U test was used for group comparisons and the Pearson correlation coefficient for correlations. The dataset was also investigated by principal component analysis using the NSE and Aβ42 (Umeå AB, Umeå, Sweden), and by partial least squares with cross validation as a validation tool for multivariate correlations between CSF biomarkers and diagnosis.

When comparing CSF biomarkers between patients with Alzheimer’s disease and controls (values given as means (SD)), there was a significant increase in CSF tau (634 (289) vs 375 (171) pg/ml), Aβ42 (425 (194) vs 295 (194) pg/ml), and in CSF NSE 615 (436) vs 295 (194) pg/ml.
In agreement with previous findings, increased CSF tau and decreased CSF Aj42 was found in Alzheimer’s disease, resulting in a good sensitivity and specificity for discriminating Alzheimer’s disease from controls. As the ability of these CSF biomarkers to discriminate Alzheimer’s disease from other dementia disorders is less than optimal, we tested whether the combined analysis of additional biomarkers for axonal degeneration (CSF NFL), neuronal degeneration (CSF NSE), and gliosis (CSF GFAP and CSF S-100β) resulted in any further increase in the diagnostic sensitivity or specificity. However, there was only a marginal increase in sensitivity (from 91.4% to 97.1%) whereas the specificity was unchanged (89.5%). Therefore we conclude that these biomarkers have little additional value as diagnostic biochemical markers for Alzheimer’s disease.

We hypothesise that other biomarkers more specifically related to Alzheimer’s disease’s disease pathogenesis, such as hyperphosphorylated tau, synapse specific proteins (for example, rab5a, synaptotagmin), or APP isoforms (for example, β-secretase cleaved APP), may have a larger potential as CSF biomarkers for Alzheimer’s disease.

This work was supported by grants from the Swedish Medical Research Council (grants 12103 and 11560); Alzheimerforden, Lund, Sweden; Stiftelsen for Gamla Tjänstebarn, Stockholm, Sweden; Tore Nilssons Fond för Medicinsk Forskning, Stockholm, Sweden; Norrbottens Läns Landstings FOU Fund, Sweden; Svenska Läkareäknenkapet, Stockholm, Sweden; and Åke Wibergs Stiftelse, Stockholm, Sweden. We are grateful to Mrs Christina Sjödin and Mrs. Maria Ländby for skillful technical assistance.

Aurell A, Rosengren LE, Karlsson JO, et al. Patients with amyotrophic lateral sclerosis and other neurodegenerative diseases have increased levels of neurofilament protein in CSF. J Neuosci 1996;16:157–64.

Variant Creutzfeldt-Jakob disease is not associated with individual abilities to metabolise organophosphates.

Since its identification as a distinct form of human prion disease, it has been demonstrated that vCJD is related to bovine spongiform encephalopathy (BSE), thus providing evidence for transmission of the disease from cattle to humans. Despite widespread beef consumption, however, the number of cases of vCJD has been low and moreover, there is no history of unusual exposure to beef or its products among affected persons. These findings may arise from a combination of factors, including the existence of environmental factors that may affect susceptibility, the long incubation period for vCJD, uneven exposure to infected beef, and variations in individual genetic susceptibility to the transmission process. Of the known genetic factors, it has been established that polymorphisms of codon 129 of the prion protein gene confer individual susceptibility to vCJD. This polymorphism is common in the normal population, suggesting that other genes contribute to genetic susceptibility to vCJD.

This study aimed to establish whether polymorphisms in the paraoxonase family of genes are associated with incidence of vCJD and was based on the hypothesis that exposure to OPs, widely used as insecticides in the United Kingdom, was causally related to the vCJD epidemic. Polymorphisms have been shown to play a major role in the detoxification of many organophosphate pesticides: PON1 allelic variants confer fast or slow abilities to detoxify these xenobiotics. PON1 is also known to protect against accumulation of potentially harmful oxidised lipids: this scavenging role of PON1 has been used to provide a rationale for the association of both PON1 and PON2 polymorphic variants with predispositions to heart disease.

The rationale for our study is also supported by the finding that, in cultured cells, the organophosphate pesticide phosmet, widely used at high doses in the United Kingdom to eradicate water hyacinths, increases cell surface levels of normal prion protein in human neuronal cells; high levels of PrP expression are themselves known to be associated with increased ease of transmission of prion diseases. Although it has been shown that vCJD does not seem to be associated with exposure to organophosphates present in head lice treatments, our study aimed to establish whether persons affected by vCJD are more genetically susceptible to organophosphate exposure than the normal population.

Using the polymerase chain reaction and restriction analysis, we genotyped 26 patients with vCJD, 19 patients with sporadic CJD, and 10 neurological controls for both codon 54 and 192 of PON1 and codon 311 of PON2 polymorphisms. In addition, we genotyped 93, 137, and 95 patients respectively for codon 54 and 192 of PON1 and codon 311 of PON2 polymorphisms.

All patients were clinically diagnosed and neuropathologically confirmed. None of the patients with vCJD that we studied belonged to the cluster recently found in Leicester.

Statistical analysis of the data was performed using the Pearson’s χ2 test (p<0.05).

The distribution of PON1 and PON2 genotypes and allele frequencies in patients and controls is shown in table 1. All genotype frequencies did not deviate significantly from the predicted Hardy-Weinberg equilibrium (data not shown). The frequency of allele L(Leu) and M(Met) at codon 54 of PON1 were respectively 0.672 and 0.328 in the control population (n=93), 0.654 and 0.346 in vCJD, 0.684 and 0.316 in sporadic CJD, and 0.776 and 0.219 in control population (n=117) in the control group. The frequencies of allele A(Gln) and B(Arg) at codon 192 of PON1 were respectively 0.726 and 0.274 in vCJD, 0.757 and 0.245 and 0.669 and 0.331 in sporadic CJD, and 0.690 and 0.310 in neurological controls. Finally, the frequencies for alleles S(Ser) and C(Cys) at codon 311 of PON 2 were respectively 0.774 and 0.226 in controls (n=95) and 0.786 and 0.213 in vCJD, 0.763 and 0.237 in sporadic CJD, and
Table 1 Distribution of PON1 and PON2 genotypes and allele frequencies in cases and controls *

<table>
<thead>
<tr>
<th>Allele</th>
<th>Controls</th>
<th>Neurological controls</th>
<th>Sporadic CJD</th>
<th>Variant CJD</th>
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<tr>
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<td>L/L(eu)</td>
<td>M(Met)</td>
<td>S(Ser)</td>
</tr>
<tr>
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<td>n</td>
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<td>4 (40)</td>
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<tr>
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<td>n</td>
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<td>6 (60)</td>
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<tr>
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<td>5 (50)</td>
<td>10 (52.6)</td>
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<tr>
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<tr>
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<tr>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Genotype</td>
<td>Allele</td>
<td>S(Ser)</td>
<td>C(Cys)</td>
<td>B(Thr)</td>
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<td>n</td>
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<td>CS</td>
<td>n</td>
<td>33 (34.7)</td>
<td>4 (40)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>CC</td>
<td>n</td>
<td>5 (5.3)</td>
<td>1 (10)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Allele</td>
<td>n</td>
<td>0.774</td>
<td>0.700</td>
<td>0.763</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages. All data were analysed using Pearson’s χ² test (significance taken as p<0.05). There were no significant differences between the cases and controls.

0.700 and 0.300 in neurological controls.

There was no significant association between any of the PON polymorphisms studied and vCJD, sporadic CJD, or the other neurological disorders (table 1). Our data show that PON polymorphic variants are not associated with vCJD. These data, together with the data of Cochell et al., indicate that exposure to organophosphates is unlikely to contribute to the incidence of vCJD.

We thank Dr Maureen Marks for statistical help and advice.

Monitoring an electroencephalogram for the safe application of therapeutic repetitive transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) has come to be widely used to evaluate the CNS since the first report on the use of TMS in humans by Barker et al. in 1985. Depending on the frequency, intensity, and duration of stimulation, trains of repetitive TMS (rTMS) can transiently block or inhibit the function of a cortical region. It has been suggested that rTMS has therapeutic potential for the treatment of Parkinson’s disease and psychiatric disorders. The directions of the electrical current of motor threshold measurement and rTMS of the ipsilateral prefrontal cortex were the same. This assessment was carried out one hour earlier than the first rTMS session. Motor threshold intensity was defined as the lowest stimulation intensity that induced five motor evoked potentials (MEPs) of 0.05 mV in peak to peak amplitude in 10 trials. Motor threshold intensities of the right and left abductor pollicis brevis muscles were 55% and 52% of the maximum stimulator output, respectively.

Left and right prefrontal cortex stimulation were defined as stimulations with the same coil centred over a point 5 cm anterior to the frontal scalp position for activation of the contralateral abductor pollicis brevis muscle. The patient agreed to participate in this trial before application of rTMS and gave informed consent to the study, which was approved by the local ethics committee.

During the application of rTMS, an EEG was recorded through F3, F4, C3, and C4, according to the International 10–20 system, in addition to monitoring MEPs on the bilateral obliquus externus abdominis muscles. Conventional EEGs recorded at rest before and after the rTMS trial did not show any abnormalities. Seizure was not seen during the measurement of motor thresholds, although an EEG was not recorded. For the purpose of avoiding skin burn, radial notched electrodes were used while recording the EEGs.

A focal slow wave (3–4 Hz) was recorded on C4 after the 4th stimulation of rTMS to the right prefrontal cortex on the first day of the trial. The slow wave disappeared at least 6 seconds later and reverted to an 8–10 Hz wave (fig 1).
prefrontal cortex was restarted, a slowing wave of the EEG recurred and lasted longer after the 4th stimulation. This change did not occur during rTMS to the left prefrontal cortex. The recurring slow wave began and disappeared in the same manner.

The patient remained alert and seizure was not seen. These changes were reproducible in an rTMS trial performed on another day. We considered that these changes were induced by the application of rTMS and immediately discontinued the trial. During measurements of motor threshold and rTMS, the involuntary movement of the trunk and lower limbs disappeared in the same manner.

The slow wave disappeared at least 6 seconds later and reverted to an 8–10 Hz wave. This change was reproducible in rTMS performed on another day.

Figure 1 Change in the EEG during rTMS. After rTMS to the right prefrontal cortex had been initiated, the EEG recorded on C4 showed a slow wave. The slow wave disappeared at least 6 seconds later and reverted to an 8–10 Hz wave. This change was reproducible in rTMS performed on another day.


Early onset epileptic auditory and visual agnosia with spontaneous recovery associated with Tourette’s syndrome

Potentially recoverable impairments of cognition, behaviour, and movement are integral to early onset epilepsies. The classic epilepsy syndrome presenting as developmental regression is Landau-Kleffner syndrome, in which receptive aphasia and behavioural, cognitive, and motor impairments occur with centromedial or centroparietal discharges enhanced in sleep. We report a novel biography of domain specific impairments and recovery in infantile spasms.

At 12 years of age the patient presented with Tourette’s syndrome, with an extraordinary developmental history of epilepsy, regression, and recovery. He was normal until 6 months, being socially responsive, visually alert, reaching and transferring objects. Development slowed from 7 months. There was no relevant family history.

At 6 months runs of typical symmetric flexion spasms at intervals of 5–10 seconds, 3–4 times/day began. The EEG was disorganised, with bilateral very high amplitude (450 µV) activity and more left temporal area multifocal spikes and polyspikes, approaching classic hypsarhythmia. ACTH (10 units daily and 40 units daily from 10–12 months) stopped the spasms after 2 weeks. Electroencephalography, CT, metabolic investigations, electroretinography, and visually evoked potentials were normal. CMV antibodies were present in blood, and virus in the urine.

Physical examination was normal. At 1 year an EEG showed excess of irregular slow activity without spikes. A sleep record was not performed.

One to two brief generalised seizures a week, consisting of slumping, losing consciousness and bilateral limb shaking, continued to 5 years of age. Occasional brief absences continued, were not treated, and stopped at 10.6 years. An EEG at 12 years was normal.

He lost smiling, visual following, and responsiveness at 7 months, 2 weeks before spasms were recognised. At 10.5 months development was assessed at a 7 month level. Development remained very slow to 3–3.5 years. At 3 years he could not understand speech or visually recognise his mother and performance skills were poor—for example, he could not thread beads. Cognition was assessed at less than half his chronological age, indicating educational needs as a child with severe learning difficulties. At 3.5 years speech understanding appeared, and by 4.5 years he was using a lot of speech. His family felt that “their child had returned”.

On the Portage scale at 2.5 years of age, the raw scores and age level were socialisation 38: 1–2 years; language 7: 0–1 years; self help 24: 1–2 years; cognitive 18: 1–2 years; motor 68: 2–3 years. Non-motor skills were below 2 years with severe language retardation.

A Griffiths assessment at 3.10 years showed significant recovery: hearing and speech 3.8 years; performance 3.6 years;
motor evoked potentials (MEPs) were elicited by cortical stimulation using a parabolic shaped coil, diameter 14 cm with a Twintop Magnetic Stimulator, and EMG responses were recorded with a Keypoint EMG-machine (Dantec Medical Inc, Denmark). The compound motor action potentials (CMAPs) were recorded from the external anal sphincter using a disposable sphincter electrode (Dantec 13L81, Dantec Medical Inc, Denmark). The position of the electrode was anteroposterior to avoid cancelling of the motor potentials because of bilateral contrac-
tion from the right and left side of the external anal sphincter induced by cortical and sacral stimulations.

The cortical stimuli were applied near to the vertex in the area representing the lowest threshold for a motor contraction in the lower limbs measured in the right arm and left arm (AH) muscle. The motor threshold (MT) was determined as the minimal stimulus intensity applied to the relevant cortical rep-

citation evoking the maximum amplitudes of action potentials of five trials with an amplitude exceeding 50 μV. In some patients the MEP amplitudes were very small, and therefore MT determination was difficult. To ensure a sufficient stimulus intensity the AH muscle was selected for MT measures. The stimulus intensity was increased to 50% above MT for the AH muscle or to a level sufficient to evoke a reproducible contraction of the external anal sphincter. The patients and the controls were instructed not voluntary to contract the sphincter (“relaxed MEPS”). The cortical latency (CL) and amplitude of the CMAP were identified. The sacral stimulation was applied to the S2-S4 area using magnetic stimulation (maximum output) and the sacral latency (SL) and the central motor conduction time (CMCT= CL-SL) were calculated. The stimulations were performed at least twice in individual trials with two runs to ensure reproducibility. In four patients the motor action potentials were hardly reproducible, and therefore an averaging technique was used in those patients. The results of MEPS

don described.4 The investigator was blinded to the urinary and bowel symptoms. The study was approved by the ethics committee.

Motor evoked potentials (MEPs) were elicited by cortical stimulation using a parabolic shaped coil, diameter 14 cm with a Twintop Magnetic Stimulator, and EMG responses were recorded with a Keypoint EMG-machine (Dantec Medical Inc, Denmark). The compound motor action potentials (CMAPs) were recorded from the external anal sphincter using a disposable sphincter electrode (Dantec 13L81, Dantec Medical Inc, Denmark). The position of the electrode was anteroposterior to avoid cancelling of the motor potentials because of bilateral contrac-
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Motor evoked potentials from the external anal sphincter in patients with autosomal dominant pure spastic paraplegia linked to chromosome 2p

Hereditary spastic paraplegia (HSP) is the name given to a heterogeneous group of rare neurodegenerative disorders of the motor system characterised by slowly progressive spasticity and weakness of the lower limbs. About one third of HSP patients exhibit autosomal dominant pure spastic paraplegia (ADPSP) linked to chromosome 2p. HSP has several subtypes and is differentiated from other causes of spasticity such as stroke, traumatic brain injury and multiple sclerosis. The clinical features are variable and include a spectrum of symptoms including gait disturbances, urinary and bowel symptoms. The study of five cases.

Figure 1 Cortical and sacral stimulation and CMAP from the external anal sphincter evoked in (A) a control person and (B) in a patient with ADPSP with LUTS and RUI. The stimulation is reproduced in three trials over the vertex and the sacral region.


Motor evoked potentials from the external anal sphincter in patients with autosomal dominant pure spastic paraplegia linked to chromosome 2p

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Figure 1 Cortical and sacral stimulation and CMAP from the external anal sphincter evoked in (A) a control person and (B) in a patient with ADPSP with LUTS and RUI. The stimulation is reproduced in three trials over the vertex and the sacral region.

CL p=0.02; CMAP amplitude p=0.03; CMCT p=0.01.

LUTS=Lower urinary tract symptoms; RUI=rectal urgency/urge incontinence; CL=cortical latency; CMAP=compound muscle action potential.

The results are presented as median (range), and the distributions were compared by the Kruskal-Wallis test. The level of significance was set at 0.05.

Examples of cortical and sacral stimulation and CMAP from the external anal sphincter evoked in a control person and in a patient with LUTS and RUI are shown in figure 1. Table 1 shows the data from these studies.

The CL and the CMCT were significantly longer and the amplitude of CMAP at cortical stimulation was significantly lower in the patients with ADPSP with LUTS and RUI compared with the patients without these symptoms. The patients without LUTS and RUI presented no significant differences in CL, CMCT, or amplitude of the CMAP compared with the controls. The patients with LUTS and RUI presented significantly longer CL and CMCT and lower amplitudes of the CMAP than the control subjects. No significant differences in SL or amplitudes of CMAP at sacral stimulation were seen between the patients with ADPSP and the controls.

In this study we found that reproducible CMAPs could be obtained from the external anal sphincter using surface electrodes with cortical and sacral stimulation. Our normative values were similar to former studies. Using TMS we showed that patients with LUTS and RUI presented longer CMCT and reduced amplitudes of the cortical evoked CMAPs, whereas patients without these symptoms showed no differences. As shown in table 1, there is little overlap between the two groups. The number of patients is small, but the results suggest that measurement of MEPs from the external anal sphincter may be a method to be used as a part of the evaluation of patients with supranuclear lesions and sphincter symptoms.

In neuropathological studies axonal degeneration was found to be maximal in the terminal portions of the longest descending and ascending tracts. Dorsal root ganglia, posterior roots, and peripheral nerves were normal. Axonal degeneration of the corticospinal neurons, however, cannot solely explain the pathogenesis of the disease. Patients without LUTS and RUI presented normal CMCTs and only non-significantly reduced CMAPs, despite the presence of severe spasticity. A reduced CMAP is suggestive of selective large fibre loss in the relevant spinal cord pathways; however, other mechanisms may be involved in the reduced CMAP including a raised cortical threshold to TMS. We conclude that MEPs from the external anal sphincter in patients with ADPSP linked to chromosome 2p with LUTS and RUI present longer CMCTs and lower CMAPs at cortical stimulation. These results may in part be related to the pathogenesis of the disease. MEPs from the external anal sphincter can be relatively easily evoked and may be a new useful method in the evaluation of patients with supranuclear lesions and RUI.

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Table 1: Results (median (range)) of cortical and sacral stimulation in patients with ADPSP and normal controls

<table>
<thead>
<tr>
<th></th>
<th>Cortical stimulation</th>
<th>Sacral stimulation</th>
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<tr>
<td></td>
<td>Latency (ms)</td>
<td>Amplitude (mV)</td>
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<tr>
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<td>ADPSP (without LUTS and RUI) (n=5)</td>
<td>26.0 (24.2–28.0)</td>
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<td>ADPSP (with LUTS and RUI) (n=6)</td>
<td>33.6 (26.5–53.3)</td>
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<tr>
<td>Controls (n=12)</td>
<td>24.0 (22.0–29.5)</td>
<td>0.16 (0.04–0.42)</td>
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</table>

LUTS=Lower urinary tract symptoms; RUI=rectal urgency/urge incontinence; CL=cortical latency; CMAP=compound muscle action potential.

Call for guidelines for monitoring renal function and haematological variables during intravenous infusion of immunoglobulin in neurological patients

Intravenous immunoglobulin (IVIg) is widely used in the treatment of some neurological conditions thought to have an underlying immune basis. Controlled studies of IVIg have demonstrated benefit in Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and dermatomyositis. Treatment with IVIg has also been beneficial in myasthenia gravis, multiple sclerosis, multifocal motor neuropathy with conduction block, polymyositis, Lambert-Eaton myasthenic syndrome, stiff man syndrome, and Rasmussen’s encephalitis.1

Various complications have been reported in the literature in association with IVIg therapy. These include headache, nausea, fever, rash, aches in the chest or limbs, anaphylaxis especially in association with IgA deficiency, leucopenia, neutropenia, autoimmune haemolytic, renal failure, thrombocytopenia, aseptic meningitis, and transmission of viral infections—for example, hepatitis C.1

The therapeutic dose of IVIg in the treatment of neurological disease has been empirically set at 2 g/kg, conventionally divided into daily doses of 400 mg/kg, although some authors have shown that a 2 day infusion of 1 g/kg is not associated with any higher incidence of side effects than the 5 day infusion.2

Despite the widespread use of IVIg in neurological centres in the United Kingdom, to our knowledge there exists no consensus for advice either on monitoring haematological and renal function in patients pretreatment and post-treatment with IVIg, nor on the merits of shorter infusion periods of IVIg. Both of these factors have considerable cost implications for the National Health Service (NHS).

We have retrospectively examined the records of 21 patients admitted to a regional neurology centre (Hurstwood Park Neurological Centre), over an 18 month period. As several of these patients had multiple courses of IVIg treatment, the records contained 71 courses of treatment, although complete haematological data pretreatment and post-treatment was only available on 35 of these.

The conditions treated included Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, and myasthenia gravis. The average age of patients was 51 years (range 22–86 years). Eight patients had indications of possible renal dysfunction (based on one or more abnormal blood urea and creatinine concentration) within 6 monthsnormal. The conditions treated included Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, and myasthenia gravis. The average age of patients was 51 years (range 22–86 years). Eight patients had indications of possible renal dysfunction (based on one or more abnormal blood urea and creatinine concentration) within 6 months of treatment. A course of treatment was only available on 35 of these.

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Our current practice, based on the results of this audit and the literature available, is to check the renal function of all patients before IVIG therapy. Those in whom the renal function is mildly abnormal (normal sodium and potassium, urea 7–8 mM, and creatinine 120–150 µM) have their renal function monitored during and 5 days after IVIG treatment and are currently receiving low sucrose or no sucrose (Octogam/Octophera) and IVIG formulations. Patients with more seriously impaired renal function are not being considered for IVIG therapy; alternative modes of treatment—for example, plasmapheresis—could be considered for this subgroup. Haematological function is also checked before IVIG therapy; if normal, no further monitoring is carried out during or after IVIG treatment. If there is evidence of mild leucopenia, neutropenia, or thrombocytopenia before IVIG, the full blood count is monitored as a baseline during treatment and once more 5 days after treatment. Patients with more severe blood derangement (platelets<100×10⁹/l, neutrophil count<1×10⁹/l, and leucocyte count<2×10⁹/l) are not being considered for IVIG therapy and again alternative modes of therapy would be considered.

A consensus statement on the recommended duration of treatment course (1–2 days × 5 days) and the requirements for blood monitoring during IVIG infusion will require further study and collaborative audit across the many neurological centres in the United Kingdom using this form of therapy. We think that the potential cost implications and side effect profile of IVIG justify a call for such a study.

We thank Professor Richard Hughes for his help in the preparation of this manuscript.

Table 1  Neurological and neuropsychological findings

<table>
<thead>
<tr>
<th>Neuropsychological test</th>
<th>Control group</th>
<th>Pallidotomy group</th>
<th>Follow up evaluation</th>
<th>Follow up evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini mental state examination</td>
<td>26.3 (3.3)</td>
<td>25.3 (3.3)</td>
<td>27.5 (2.2)</td>
<td>27.5 (2.2)</td>
</tr>
<tr>
<td>UPDRS motor score</td>
<td>10.8 (5.3)</td>
<td>10.8 (5.3)</td>
<td>18.8 (15.8)</td>
<td>15.1 (9.0)</td>
</tr>
<tr>
<td>Levodopa dosage</td>
<td>390 (346)</td>
<td>390 (346)</td>
<td>890 (711)</td>
<td>890 (711)</td>
</tr>
<tr>
<td>Raven’s progressive matrices</td>
<td>59.8 (36.5)</td>
<td>59.8 (36.5)</td>
<td>622 (34.3)</td>
<td>622 (34.3)</td>
</tr>
<tr>
<td>Wisconsin card sorting test</td>
<td>2.7 (2.4)</td>
<td>2.7 (2.4)</td>
<td>2.7 (2.4)</td>
<td>2.7 (2.4)</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>40.9 (9.9)</td>
<td>40.9 (9.9)</td>
<td>40.9 (9.9)</td>
<td>40.9 (9.9)</td>
</tr>
<tr>
<td>Buschke total recall</td>
<td>65.4 (22.2)</td>
<td>69.4 (17.5)</td>
<td>76.7 (18.1)</td>
<td>70.5 (13.3)</td>
</tr>
<tr>
<td>Buschke delayed recall</td>
<td>56.6 (20.9)</td>
<td>56.6 (20.9)</td>
<td>6.8 (3.0)</td>
<td>6.8 (3.0)</td>
</tr>
<tr>
<td>Benton visual retention test</td>
<td>7.7 (2.0)</td>
<td>7.7 (2.0)</td>
<td>7.7 (2.0)</td>
<td>7.7 (2.0)</td>
</tr>
<tr>
<td>Digits forward</td>
<td>5.7 (1.1)</td>
<td>5.7 (1.1)</td>
<td>5.6 (0.9)</td>
<td>5.6 (0.9)</td>
</tr>
<tr>
<td>Digits backward</td>
<td>4.2 (1.0)</td>
<td>4.2 (1.0)</td>
<td>4.4 (1.0)</td>
<td>4.4 (1.0)</td>
</tr>
<tr>
<td>Perdue pegboard test*</td>
<td>19.3 (5.5)</td>
<td>18.9 (6.4)</td>
<td>19.3 (5.5)</td>
<td>18.9 (6.4)</td>
</tr>
</tbody>
</table>

Values are means (SD). *P<0.01, **P<0.001.

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Neuropsychological effects of pallidotomy in patients with Parkinson’s disease

Whether patients with Parkinson’s disease develop cognitive impairments or improvements after ventral pallidotomy is still a debated issue. Recent studies produced contradictory findings which may have resulted from methodological factors such as differences in surgical techniques, neuropsychological assessments, duration of follow up, and the lack of evaluations of non-operated controls with Parkinson’s disease.

We assessed a consecutive series of 27 patients with Parkinson’s disease who received unilateral pallidotomy using the microelectrode registration technique. Sixteen of these patients received a 3–6 month follow up evaluation, and 11 of them received a 12 month follow up evaluation. They were compared with a non-operated control group of 20 patients with Parkinson’s disease matched for age, severity of extrapyramidal symptoms, and overall cognitive status who received the same neuropsychological evaluation at baseline and 12 months later. The neuropsychological examination included the Raven’s progressive matrices, the Wisconsin card sorting test (WCST), the controlled oral word association test, the Buschke selective reminding test, the Benton visual retention test, the digit span, and the Perdue pegboard.

No significant differences between the pallidotomy and the control groups were found for age (years (SD) pallidotomy group 56.3 (6.9), control group 59.3 (7.9)), sex (pallidotomy group 50% women, control group: 50% women), education (years) (SD) pallidotomy group 10.7 (2.7), control group: 11.4 (4.1)), baseline levodopa equivalent dosage, and UPDRS total scores (table 1). All patients were right handed.

Sixteen patients with Parkinson’s disease who underwent unilateral pallidotomy received a 3–6 month follow up. A repeated measures multivariate analysis of variance (MANOVA) for the neuropsychological variables comparing baseline versus 3–6 month
follow up evaluation showed no significant overall time effect (F(7,56)=1.01; NS). There was a significant time effect for the Perdue pegboard test (F(1,14)=30.9; p<0.0001), with a significant improvement in manipulative dexterity over time. A repeated measures MANOVA for the neurophysiological variables comparing patients with either a left (n=7) or right (n=9) pallidotomy showed no significant group effect (F(1,7)=0.85; NS), time effect (F(1,7)=1.03; NS), or group-time interaction (F(6,56)=0.22; NS).

A repeated measures MANOVA for the neurophysiological variables for the 10 patients who had undergone pallidotomy (six right, four left) with a 12 month follow up and the 20 non-operated patients with Parkinson’s disease did not show a significant group effect (F(1,23)=0.29; NS), time effect (F(1,23)=0.48; NS), or group-time interaction (F(7,161)=0.18; NS). On the other hand, there was a significant group-time interaction for the Perdue pegboard test (F(1,28)=8.84; p<0.01), the pallidotomy group showed a significant improvement during the follow up period, whereas the control group had a slight decline.

Most studies on the cognitive sequelae of pallidotomy could not show significant neuropsychological effects after surgery, and the only studies that to our knowledge included a non-operated Parkinson’s disease control group (Perrine et al. and the present one) confirmed this finding. On the other hand, Lang et al. reported some cognitive impairments after ventral pallidotomy; and differences in neuropsychological outcome measures may account for this discrepancy. We did not find neuropsychological sequelae of pallidotomy in a consecutive series of 16 patients with Parkinson’s disease, 10 of whom had a 1 year follow up evaluation. When compared with a group of 20 patients with Parkinson’s disease matched for MMSE scores and age who did not receive a pallidotomy, no significant between group differences were found in the rate of cognitive changes. On the other hand, the pallidotomy group showed a significant improvement on a task measuring manual dexterity compared with the control Parkinson’s disease group. The question now arises as to why pallidotomy patients were tested three or four times, compared with only two neuropsychological evaluations for the control group, which may have produced some learning effects.

This study was partially supported by a grant from the Raul Carrea Institute of Neurological Research-FLENI and the Fundación Puenzo Py Company. We thank Fred Bylsma PhD for his useful suggestions.

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Response to botulinum toxin in a case of rigid spine syndrome

First described by Dubowitz in 1965,2 rigid spine syndrome represents an axial congenital merosin positive muscular dystrophy with early, predominant rigidity of the spine as its main characteristic trait. The illness begins at an early age with a delay in motor development, and affects more boys than girls; however, in some cases onset occurs slightly later when weakness of proximal limb muscles appears in a previously otherwise asymptomatic child. In all cases a limitation of neck and trunk flexion develops and scoliosis appears either simultaneously or in the ensuing years; later on the disease may progress slowly or tend to stabilise. Other features that accompany the musculoskeletal signs are respiratory disturbances and cardiac changes.3,4

Recently, a few loci for this syndrome has been identified on chromosome 1p.1 In laboratory studies serum creatine kinase concentrations can be raised. Electromyographic studies of paracervical muscle ture, trapezius, deltoid, biceps, and quadriceps show a myopathic pattern with normal nerve conduction velocities. Biopsy findings disclose non-specific myopathic changes with descriptions of type I fibre predominance, type II fibre predominance and fibre type disproportion; electron microscopic studies have detected the presence of Z band streaming.

It is important to distinguish rigid spine syndrome from other diseases in which rigidity of the spine can appear, such as Duchenne and Becker’s muscular dystrophies, which are characterised initially by spastic paraparesis and later on by stiffness and scoliosis; and from other neurodegenerative and progressive diseases such as nemaline myopathy. As in other muscular dystrophies, no more than supportive care can be offered to patients with rigid spine syndrome; surgical correction has been attempted on one occasion with success.5 Here we report a good response to botulinum toxin type A (BOTOX) treatment in a young man with rigid spine syndrome.

A 19 year old boy born at term, with congenital hypotonia and normal psychomotor development, was being studied by an endocrinologist because of short stature (mother’s stature 145 cm, father’s stature 169 cm) who noticed progressive increase in body mass and was referred to our institution. At admission on 8 July 1996, he complained of back pain since the previous year, which was more severe at rest; his father had noticed a gait disturbance, and that his back was progressively bending forward. General examination was normal; neurological examination showed no abnormal findings, and strength was completely preserved in all four limbs. He had normal postural kypnosis and contracture of neck extensors severely limiting movement in the anterior and lateral senses; hip flexion was severely affected (below 30°); no pain was produced by sacral manoeuvres. Radiological examination of the cervicothoracic spine showed scoliosis without vertebral malformations, 65° cervical lordosis involving C2 to C7, and a 55° thoracic kyphosis involving T3 to T12. Routine blood testing showed no abnormalities and creatine kinase concentrations were normal; autoantibodies routinely tested were negative. Complete spine MRI studies ruled out vertebral malformations. An ECG and radiography of the chest were normal. Radiological study of sacral joints was normal and the patient was not HLA-B27 positive. An EMG study showed a myopathic pattern (paraspinal muscles). He had mild myopathies such as nemaline myopathy, and right quadriiceps with

| Table 1 Schedule, place, and amount of botulinum toxin injection |
|-----------------|-----------------|-----------------|-----------------|
| Injected muscle | July            | August          | September       |
| Trapezius       | 50 IU BOTOX*    | 30 IU BOTOX*    | 20 IU BOTOX*    |
| Eternocleidomastoid (ECM) | 30 IU BOTOX* (right trapezius) | 20 IU BOTOX* (right trapezius) | 10 IU BOTOX* (right trapezius) |
| Paracervical muscle | 30 IU BOTOX* (ECM) | 20 IU BOTOX* (ECM) | 15 IU BOTOX* (ECM) |

*The patient received 50 IU BOTOX* (Allergan) in three different locations of each trapezius on 17 July 1996; on 24 October 1996, 30 IU BOTOX were administered in each eternocleidomastoid and 30 IU in right trapezius; on 22 January 1997 30 IU BOTOX were given in each eternocleidomastoid and trapezius; on 21 May 1997 20 IU BOTOX were given in each trapezius; on 25 September 1997 40 IU BOTOX were given in each trapezius and bilateral paracervical muscle (total 80 IU); on 15 January 1998 10 IU BOTOX were given in each trapezius and 30 IU in paracervical muscle bilaterally.

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no abnormalities in nerve conduction. A biopsy of paraspinal musculature was performed and the neuropathological study of the muscle showed non-specific myopathic changes, including slight variability in muscle fibre size, occasional moth eaten fibres, and dilatations of the smooth endoplasmic reticulum, which were filled with fine granular material. The distribution and percentage of fibre types was preserved and no abnormalities in mitochondria and myofibres were seen. Immunohistochemistry to dystrophins, utrophin, and spectrin was normal. A diagnosis of rigid spine syndrome is not well understood. Shortening of paraspinal ligaments or shortening of muscle fibres due to myofibrilar disorganisation have been invoked as possible origins of stiffness; weakness of neck fibres can make this group of muscles incapable of counteracting extensor strength, finally causing spinal rigidity and cervical lordosis. Botulinum toxin may have an important part to play in preventing development of contractures and avoiding stiffness, not only in a symptomatic way, but also in a curative manner, as in our patient.

We thank Ms Julie Myers and Mr Josep Gracols for linguistic assessment.

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**Figure 1** Three different photographs in which progressive amelioration in neck flexion is seen. To make this change objective, we measured the angle between a line joining nasion and tragus and another prolonging the sternum surface. (A) Photograph taken on 22 January 1997. (B) Photograph taken on 24 September 1997. (C) Photograph taken on 15 January 1998.

Brain MRI is an important tool in the investigation of patients with unusual Parkinsonian syndromes. The “hot cross bun” sign is a radiological sign which has been said to be highly specific for multiple system atrophy. However, we now report on a patient with the hot cross bun sign who presented with parkinsonism secondary to presumed vasculitis.

Our patient was a 31 year old woman who was referred with an 18 month history of double vision, balance problems, and deafness. Brain MRI performed 9 months before this admission had demonstrated a non-enhancing swelling of the pons (fig 1 A). She had not responded to a 4 week course of oral adrenocorticotropic hormone treatment at that time. On admission to our unit there had been no change in her symptoms. On examination she had mild cognitive impairment (mini mental state score 24/30) and a labile affect. She had a bilateral horizontal supranuclear gaze palsy. In addition she had a right upper motor neuron facial palsy and bilateral sensorineural deafness (confirmed by audiometry). Examination of her limbs showed axial and bilateral limb rigidity. She exhibited bradykinesia but did not have a resting tremor. She had signs of cerebellar ataxiaorage her limbs and walked with a broad based gait requiring the assistance of another person. Limb power and sensation were normal and her plantars were flexor. There was no evidence of dysautonomia or rheumatological disease.

Blood investigations showed a raised erythrocyte sedimentation rate at 36 mm/hour, raised serum IgG at 21.7 g/l (normal pattern on electrophoresis), a positive rheumatoid factor titre (1:320), a positive speckled ANA titre (1:640), and positive anti-Ro antibodies (33 units). Scharmer’s test, thyroid function tests, copper studies, and manganese were all negative or normal. Brain MRI showed severe atrophy of the medulla,pons, cerebellum, and middle cerebellar peduncles with cross shaped T2 signal hypointensity within the pons (hot cross bun sign) and high signal change in the middle cerebellar peduncles (fig 1 B). There were no supratentorial lesions. Phase contrast MR angiography of the brain was normal. Examination of CSF showed no increase in cells
and normal protein, lactate, and glucose; however, CSF electrophoresis demonstrated intrathecal oligoclonal IgG production. The patient was treated with pulsed intravenous cyclophosphamide and a reducing course of steroids but did not improve significantly. There has been no further deterioration since treatment.

The hot cross bun appearance in multiple system atrophy is due to loss of pontine neurons and myelinated transverse pontocerebellar fibres with preservation of the corticospinal tracts which run craniocaudally. Our patient presented with a severe parkinsonian syndrome associated with cerebellar and brain stem dysfunction. The absence of dysautonomia together with the initial MRI appearance of swelling of the pons made the diagnosis of multiple system atrophy extremely unlikely. Although she had a supranuclear gaze palsy her scans were not typical of progressive supranuclear palsy. The pathological and CSF findings together with initial pontine swelling suggested probable vasculitis, a recognised cause of parkinsonism.

Wallerian degeneration secondary to vasculitic infarction results in hyperintensity on T2 weighted MRI. The hot cross bun sign in our patient may reflect selective wallerian degeneration of transverse pontocerebellar fibres. Thus, the clinical findings of this case highlight the need to consider alternative diagnoses to multiple system atrophy in patients with the hot cross bun sign.

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**BOOK REVIEWS**


Charcot-Marie-Tooth disease. A practical guide, is a book compiled by CMT International UK with the aim of providing an overview of Charcot-Marie-Tooth disease (CMT) with a particular emphasis on providing practical day to day advice for living with the disease. It is aimed at doctors and patients and other professionals who will help patients. All three sections provide a very useful guide, full of useful information and contacts.

It will be a particularly useful book to recommend to newly diagnosed patients.

MARY REILLY


This is an extremely interesting and informative book that does justice to the complexity of perspectives on child and adolescent conduct problems. It is evident that considerable attention was given to shaping this book, which succeeds in being more than a collection of papers on conduct problems. Individual authors have been careful to introduce their particular area of interest to readers unfamiliar with their field. For example, Herbert and Martinez’s chapter on “Neural mechanisms underlying aggressive behaviour” is a lucid account and available to the novice reader. Throughout the book there are discussions that refer to other theoretical perspectives, thus illuminating the theoretical, methodological, and clinical issues. Reading the book is rather like a mental brass rubbing in that the reader’s patience is rewarded by the emergence of an increasingly complex but fascinating pattern of relations between biological, genetic, neuropsychological, social, interational and psychological stand points.

The book moves back and forth between chapters that contextualise, for example the historical perspective offered by Costello and Angold’s chapter, to consideration of very specific mechanisms such as Lynham and Henry’s chapter on the role of neuropsychological deficits and Pett, Polha, and Mize’s chapter on perceptual and attributional processes. Each chapter gives a critical view of relevant research and raises methodological concerns. The spirit of the book is captured in Hill’s chapter on biosocial influences, in which he conveys a sense of the interaction between biological and social phenomena and how that might be further investigated.

Kazdin gives careful attention to treatment of conduct disorders in an excellent chapter. Le Marquand, Tremblay, and Vitario consider issues of prevention and Knapp’s chapter brings forward the economic costs of conduct disorder.

In conclusion I return to the subjects of this work, the children and young people, and their families who experience great emotional distress and difficulty, very often in the context of socioeconomic hardship. Inclusion of qualitative research would have further enriched this book, by bringing their voices more directly into the important debates so elegantly presented. It deserves to become a standard work, available widely to all clinicians and researchers interested in this field.

MOIRA DOOLAN


This short book describes the fascinating recovery and remarkable neurocognitive compensation of Nico, a little boy who at the
Neurobehavioural disability and social handicap following traumatic brain injury—overall the book revisits important generalisations and speculations that Battro successfully succeeds in making for an intriguing and readable book—namely that “Brain injury genetics, particularly those of occipital origin. It is a tremendously useful source book for both the literature and clinical examples of this group of disorders and more than half of the chapters are devoted to the occipital epilepsies. Dr Panayiotopoulos puts forward the view that the benign childhood partial seizure disorders should be regarded as one common genetically determined functional derangement but the case for this except in the broad phenotypic classification sense is not made. He thinks that his proposed name of benign childhood (occipital centrotemporal, frontal) seizure susceptibility syndrome has not been taken up in the way in which he would have liked. Some early parts of the book on how to manage a neurophysiology department are not strictly relevant to the main purpose. The historical insights into these conditions are fascinating and Dr Panayiotopoulos is to be congratulated on providing a tremendously valuable analysis of this huge literature, which will be used by those working with the developmental epilepsies.

BRIAN GR NEVILLE


The issue of quality of life in epilepsy has developed enormously over the past 10 years. Although this is still rather belated in relation to other conditions where the issue has been around for much longer, there is a healthy debate ongoing about what indeed is quality of life and it is likely that no answer to this question will ever be forthcoming. Nevertheless, in terms of health outcome research, there is a place for quality of life measurement.

LEY SANDER

Epilepsy, perhaps more than any other medical disorder, is associated with profound deleterious psychological and sociological consequences that are not always directly related to the actual disease process. Instead, severe disability results from the fear that an epileptic seizure might occur at some time in the future and from the negative public image associated with the diagnosis itself. People with epilepsy, who may be perfectly normal apart from the fact that epileptic seizures occur or might occur from time to time, are commonly subjected to limitations on their daily activities ostensibly to protect them or others from injury or even death. Seizures can occur without warning, which fosters a sense of insecurity that affects social development. Opportunities for satisfying interpersonal relationships are further compromised when seizures begin in childhood and parents adopt an overprotective attitude that prevents the acquisition of skills required for a full independent life. All these introduce disabili-
ties, which potentially threaten the quality of life of people with epilepsy.

In the past decade, instruments to measure quantitatively the health related quality of life in epilepsy have been developed. Consequently, today in most major epilepsy centres, effectiveness of treatment is no longer measured only by frequency of seizures. The impact that treatment has had on the patients’ perception of improvement and their predication and vital capacity to live independent fulfilling lives are important considerations.

This book, edited by two of the leading workers in this field, is a good review of what is going on in the field of measurement of quality of life. It is comprehensive, covering almost every aspect of this domain. An excellent review of currently available quality of life measures is one of the highlights of the book. Chapters covering quality of life issues for children, adolescents, and older people with epilepsy as well as people with learning disabilities and epilepsy are also present. This book would not doubt enhance the library of any person with an interest in measuring outcome in epilepsy.

LEY SANDER

CORRECTION


In paragraph 2, left column, p 428, the word "idiopathic was misplaced during the editorial process. The paragraph should read: “The role of inheritance in epilepsy is traditionally categorised according to the mechanism of inheritance: (1) mendelian disorders in which the epilepsy forms part of the phenotype; (2) idiopathic epilepsies with mendelian inheritance; (3) idiopathic epilepsies with complex inheritance; (4) epilepsies associated with cytogenetic abnormality.”