LETTERS TO THE EDITOR

Very early onset Alzheimer's disease with spastic paraparesis associated with a novel presenilin 1 mutation (Phe237Ile)

Mutations in the presenilin 1 (PS1) gene (PS1) are responsible for 30%–40% of early onset familial Alzheimer’s disease and have been found so far. Phenotypic variations among mutations on PS1. Three PS1 mutations, deletion of exon 9 with and without splice acceptor site mutations, and Arg278Thr have been reported to be associated with Alzheimer’s disease with spastic paraparesis.1,2 We report clinical and genetic features of a man who developed very early onset Alzheimer's disease with spastic paraparesis, which was associated with a novel mutation of PS1, Phe237Ile.

A 35 year old Japanese man had graduated from a national university and had worked as a psychiatric counsellor for a local clinic. His first neurological symptom was gait disturbance at the age of 31. At the age of 32, mild memory impairment and decreased mental activity were noted. His neurological deficits progressed gradually. On neurological evaluation at the age of 33, diffuse hyperreflexia, ataxia in all limbs, bilateral Babinski's sign, and dementia (total IQ on the WAIS-R of 75) were noted. He gave up his job at this time. At the age 34, he could not live alone because of memory deficit and cognitive dysfunction (total IQ on the WAIS-R of 59). At the age of 35, he became bedridden due to deterioration of spastic paraparesis, and presented with partial or generalised seizures a few times. His parents (66 and 63 years old) and sibling (27 years old) had no neurological deficits. There was no similar disease in other members of his family. On admission, he was alert and oriented for place, but not for time. He had severe difficulties in immediate and delayed recall of presented materials. He could not answer his name and occupation, but could sometimes follow three step commands. He spoke only two word sentences and could not write any words. He also had difficulties in speech comprehension. His score on the mini mental state examination was 5. Cranial nerves were normal except for dysarthria. Deep tendon reflexes were hyperactive and plantar responses were extensor bilaterally. Muscle tone was rigid and spastic in all limbs. He had neck dystonia. No apparent weakness was noted. He presented generalised bradykinesia. He had myoclonic involuntary movement in his face and arms. Sensation remained intact. There was no remarkable abnormality in coordination. He was incontinent of urine. The protein concentration in CSF was increased at 73 mg/l whereas the cell count was normal. The concentrations of neuron specific enolase (23.6 ng/ml) and tau protein (722 pg/ml) in CSF were increased. An EEG showed generalised slowing with background theta. Somatosensory evoked potential was normal. Brain MRI showed diffuse cerebral cortical atrophy. PET with 2-18F-fluoro-2-deoxy-D-glucose as a ligand and a Tc-99m-ECD SPECT study demonstrated remarkable hypometabolism and hypoperfusion in the bilateral temporoparietal areas including the primary sensory and motor cortex, respectively.

Genomic DNA was extracted from blood. The whole coding exons of PS1 and prion protein gene (PRNP), exon 16 and 17 of the amyloid β protein precursor gene (APP), and splice acceptor site of intron 8 were amplified using a polymerase chain reaction (PCR) with primers previously described.3,4 Sequencing of both the sense and complementary strand of the PCR product were performed by ABI PRISM model 310 using the ABI PRISM BigDye Terminator cycle sequencing ready reaction kit (Perkin-Elmer, CA, USA). 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).5 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’-GTTACCT GGCCTGCTTATCTGCCT -3’, antisense primer: 5’-GGGATTTGGAAAGGCCTGGA AATG-3’). The PCR product was analyzed.

![Figure 1: DNA sequence of exon 7 of PS1 of our patient and wild type. The patient has T to A transition at the first position of codon 237 leading to the Phe237Ile mutation.](https://www.jnnp.com)

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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 site 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 16 and 17. 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 authenticate the relation between genetic abnormality and development of the disease. However, we suppose that the PS1 Phe237Ile is responsible for pathogenesis of our patient for five reasons.

Firstly, mutation in 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-Alzheimer-related conditions in 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 Leu253Pro developed Alzheimer’s disease at age 31 years.19 This patient and his patients with Met233Thr in their early 30s.1,2 Our patient also manifested his first neurological symptom at the age of 31.

Thirdly, three mutations of PS1, loss of exon 9, and without mutation in splice acceptor site mutation, and Arg278Thr are associated with Alzheimer’s disease with spastic paraparesis.1,8,17

Forthly, PEX2 examination showed hypometabolism in the temporoparietal lobes, which is a typical metabolic deficit of Alzheimer’s disease. The similar pattern of hypometabolism was reported in the patient with variant Alzheimer’s disease with spastic paraparesis.18 The result of the SPECT study was also compatible with diagnosis of Alzheimer’s disease.

As the combination of five reasons as mentioned above is hardly explained by chance, we suppose that our clinical and genetic findings would be sufficient to diagnose our patient as having Alzheimer’s disease with spastic paraparesis associated with the PS1 Phe237Ile mutation. We should examine genomic DNA and mRNA of PS1 from the patient with dementia and spastic paraparesis, even if it is an apparent sporadic case. Further collection of similar cases would establish clinical characteristics of Alzheimer’s disease associated with the PS1 Phe237Ile mutation.

The study was supported in part by a Health Science Research Grant (to MY) from the Ministry of Health and Labour, Japan, and Grants-in-Aid for Scientific Research (to HM and MY) from the Ministry of Education, Science, Sports, and Culture, Japan.

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Evaluation of CSF biomarkers for axonal and neuronal degeneration, gliosis, and β-amyloid metabolism in Alzheimer’s disease

Although the accuracy of the clinical diagnosis of Alzheimer’s disease is around 75%–90%, it is probably considerably lower early in the disease course, when symptoms are vague. Therefore, in view of potential future disease modifying compounds there is a great need for reliable diagnostic biochemical markers for Alzheimer’s disease in CSF.

Such markers should reflect the central pathognomonic processes of the disease, such as the disturbance in the metabolism of β-amyloid (Aβ) with subsequent Aβ deposition in senile plaques, the hyperphosphorylation of tau protein with subsequent formation of neurofibrillary tangles, neuronal degeneration, and gliosis.

Two promising biomarkers are tau protein (reflecting neuronal and axonal degeneration) and Aβ42 (reflecting disturbances in Aβ metabolism and possibly the clearance of senile plaques). The ability of the combination of CSF tau and CSF Aβ42 to differentiate Alzheimer’s disease from normal aging and depression is high, about 85%, also early in the course of the disease.1 Similarly, most degenerative neurological disorders have normal concentrations. However, the specificity against other dementias is not optimal.1 Thus, there is a need for additional CSF biomarkers for Alzheimer’s disease, to further increase the diagnostic accuracy.

We therefore examined whether the addition of other CSF biomarkers (two neuronal and two giall proteins) would add further to the diagnostic ability to identify Alzheimer’s disease. The neuronal proteins were neurofilament protein light subunit (NFL), the major protein component of neurofilaments (probably reflecting degeneration of myelinated axons) and neuron specific enolase (NSE), a neuronal glycolytic enzyme (probably reflecting degeneration of neuronal cell bodies). The glial proteins were glial fibrillary acidic protein (GFAP), an astrocyte specific protein considered to be the major component of glial filaments in reactive astrocytes, and S-100β, a calcium binding protein also found in astrocytes (both reflecting gliosis).

From the longitudinal geriatric population study in Piteå, Sweden we studied 35 patients with Alzheimer’s disease, mean age 72.1 (SD 5.9) years, duration of disease of 48.9 (SD 32.0) months, and with MMSE scores 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, NFL, GFAP, and S-100β. TheNSE in CSF was determined using a commercial ELISA from AB Sangtec Medical, Umeå, 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 SIMCA software (Umetri 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 (288) vs 375 (171) pg/ml), and in CSF NFL (615 (450) vs 295 (194) pg/ml).
and controls. The sensitivity using all CSF biomarkers to discriminate between Alzheimer’s disease and controls, showed a relation (loading in principal component 2). Bottom: Interindividual scores of included study objects for principal components 1 and 2 from partial least squares-DA. The principal components were derived by a projection of assessed CSF protein concentrations (included protein assessment as in the figure above). Filled circles=Alzheimer’s disease; open squares=healthy controls.

\[ p=0.002. \]

There was also a significant decrease in CSF Aβ42 in patients with Alzheimer’s disease compared with controls (748 (297) vs 1623 (429) µg/ml; \( p<0.0001 \)) and a slight but significant decrease in CSF S-100β (1.8 (0.9) vs 2.5 (0.9) µg/l; \( p=0.014 \)). By contrast, there were no significant differences in CSF-NSE (7.4 (2.7) vs 6.9 (2.1) µg/l; \( p=0.568 \)) or CSF GFAP (860 (297) vs 717 (250) ng/l; \( p=0.097 \)).

The combination of CSF tau and CSF Aβ42 gave the best sensitivity of 32/35 (91.4%) and a specificity of 17/19 (89.5%). A partial least squares analysis with all CSF biomarkers and clinical groups (Alzheimer’s disease and controls), showed a relation between a diagnosis of Alzheimer’s disease and high CSF tau, high CSF NFL, high CSF GFAP, and low CSF Aβ42 concentrations (fig 1). The NSE and S100B in CSF showed no discriminative power so these additional biomarkers gave no further aid in the discrimination between Alzheimer’s disease and controls. The sensitivity using all CSF biomarkers was 34/35 (97.1%) and the specificity was 17/19 (89.5%).

In agreement with previous findings, increased CSF tau and decreased CSF Aβ42 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%). Therefor 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 pathogenesis, such as hyperphosphorylated tau, synapse specific proteins (for example, rab5a, synaptotagmin), or APP isoforms (for example, APP, a decrease in 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); Alzheimerfonden, Lund, Sweden; Stiftelser for Gamla Tjänarinnor, Stockholm, Sweden; Tore Nilsons Fund (Örebro, Sweden, Stockholm, Sweden; Norrbottens Läns Landstings FoU Fund, Sweden; Svenska Läkarealliansen, Stockholm, Sweden; Ake Wibergs Stiftelse, Stockholm, Sweden. We are grateful to Mrs Christina Sjödin and Mrs. Maria Ländby for skilful technical assistance.

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3 Andersen A, Rosengren LE, Wikkelsö C, et al. Variant Creutzfeldt-Jakob disease is not associated with individual abilities to metabolise organophosphates.

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 prohibition, 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. However, this polymorphism is common in the normal population, suggesting that other genes contribute to genetic susceptibility to vCJD.

This study aimed to identify whether polymorphisms in the PON1 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. It was hypothesised that 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 protection 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 warble fly, upregulates 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, and 95 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 Leicestershire.

Statistical analysis of the data was performed using the Pearson’s \( \chi^2 \) test (\( p<0.05 \)). The distribution of PON1 and PON2 genotypes and allele frequencies in patients and controls is shown in table 1. Allele frequencies did not deviate significantly from the predicted Hardy-Weinberg equilibrium (data not shown). The frequencies of allele L(Leu) and M(Met) at codon 54 of PON1 were respectively 0.672 and 0.328 in the control population (\( \chi^2=9.3 \), 0.654 and 0.346 in vCJD, 0.684 and 0.316 in sporadic CJD, and 0.758 and 0.212 in neurological controls. The frequencies for alleles A(Gln) and B(Arg) at codon 192 of PON1 were respectively 0.726 and 0.274 (\( \chi^2=117 \)) in the controls, 0.731 and 0.269 in vCJD, 0.737 and 0.263 in sporadic CJD, and 0.711 and 0.289 in neurological controls. Finally, the frequencies for alleles S(Ser) and C(Cys) at codon 311 of PON2 were respectively 0.774 and 0.226 in controls (\( \chi^2=9.9 \), 0.769 and 0.231 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>Genotype</th>
<th>Controls</th>
<th>Neurological controls</th>
<th>Sporadic CJD</th>
<th>Variant CJD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LL</td>
<td>38 (40.9)</td>
<td>4 (40)</td>
<td>7 (36.8)</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>LM</td>
<td>49 (52.7)</td>
<td>6 (60)</td>
<td>12 (63.2)</td>
<td>18 (69.2)</td>
</tr>
<tr>
<td>MM</td>
<td>6 (6.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>93</td>
<td>10</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L(Leu)</td>
<td>0.672</td>
<td>0.700</td>
<td>0.684</td>
<td>0.654</td>
</tr>
<tr>
<td>M(Met)</td>
<td>0.328</td>
<td>0.300</td>
<td>0.316</td>
<td>0.346</td>
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</tbody>
</table>

Values in parentheses are percentages. All data were analysed using Pearson's 2 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,6 indicate that exposure to organophosphates is unlikely to contribute to the incidence of vCJD.

We thank Dr Maureen Marks for statistical help and advice.

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prefrontal cortex was restarted, a slowing wave of the EEG occurred 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 continued and was unchanged. We could not assess the efficacy of rTMS for involuntary movement, because the trial study was discontinued in the middle of the protocol.

The slow wave activity was not present on the adjacent recording site. A possible explanation for our findings is that the spatial variation of the magnetic field intensity acting on the cortex may have resulted in an all or none response by the neurons. Another possibility is that neurons located in a responsive cortical region may have been more sensitive to the electric current induced by rTMS.

In the guidelines for rTMS, monitoring an EEG is only a recommendation. In some case studies, the relation between seizures and EEG changes was investigated. In most of those cases, the EEGs obtained immediately after the seizures showed slowing waves, but, they normalised within 1 or 2 days. In our case, a slow wave was seen without any accompanying clinical symptoms. However, we could not rule out the possibility of a consequent seizure if the rTMS trial had been continued in this patient. These findings suggest that further investigations of EEG changes during rTMS are required to apply rTMS safely.

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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.

At 8 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 hypersynchrony. ACTH (10 units daily and 40 units daily from 10–12 months) stopped the spasms after 2 weeks. Electroencephalography, CT, metabolic investigations, electroradiography, 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 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;
locomotor 2.7 years; eye-hand coordination 2.8 years; personal/social 3.1 years.

He transferred from special to mainstream education. Coordination problems continued.

He made good academic progress but with behavioral difficulties. Psychometric testing at 12 years showed above average performance and superior language scores with slow handwriting. He passed seven GCSEs and three A levels.

He had early problems with chewing and feeding, difficulties with drawing, buttons and laces, toiletting, and in using a knife and fork. Walking and running were abnormal and he could not use a bicycle. He showed slurred speech, abnormal movements, difficulty with manual gesture imitation, difficulty accessing hip movements, brisk tendon reflexes, and a few beats of clonus at the ankle. The motor picture was dominated by dyspraxia.

From year 2 he was restless with different compulsions—for example, switching lights on and off, scratching his teeth and nose, tooth grinding, hand fiddling, and face and shoulder movements. At 12 years, he had typical complex tics of his head, face and hands, and spasms, sometimes painful, of the jaw, legs, and abdomen. Vocalisations were either unintelligible and/or repeated words—for example, “zip”.

Brain MRI at 12 years was normal.

Three features suggest a good outcome for this child with an otherwise typical presentation with infantile spasms: late age of onset, transient response, and the lack of preexisting pathology. Severe language impairment at 2.5 years might suggest a variant of Landau-Kleffner syndrome (acquired epileptic aphasia), but atypically with very early onset and severe language impairment but if later there is potential for recovery. During the prolonged phase of “agnosia” information seems to have been acquired but was not accessible. The comorbidity of Tourette's syndrome is unexplained.

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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 patients with autosomal dominant pure spastic paraplegia (ADSPD) linked to chromosome 2p have lower urinary tract symptoms (LUTS) and additionally most of them also experience rectal urgency/incontinence (RUI) as well as sexual dysfunction.

The direct motor pathway to the external anal sphincter may be studied by transcranial magnetic stimulation (TMS), evoking compound muscle action potentials (CMAPs) with cortical and sacral stimulation. This study was conducted to evaluate the motor evoked potentials (MEPs) from the external anal sphincter in patients with ADSPD linked to chromosome 2p and to obtain normative data.

After informed consent was obtained 11 definitely affected patients from six different families with ADSPD linked to chromosome 2p and 12 normal controls were included. The median age for the patients was 41 (range 20–64) years, and for the controls 40 (range 21–60) years. Six patients had LUTS and RUI, five patients had previously undergone urodynamy evaluation including measures of the bulbocavernous reflex (patient numbers A2, C4, C6, K10, and L1 in Neerup Jensen et al). Five patients were without LUTS and RUI. Family details, clinical features, and urodynamy findings have been previously described. 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 obtained 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 13BL1, Dantec Medical Inc, Denmark). The position of the electrode was anteroposterior to avoid cancelling of the motor potentials because of bilateral contraction 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 ankle (AH) muscle. The motor threshold (MT) was determined as the minimal stimulus intensity applied to the relevant cortical representation evoking at least seven motor 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, 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
part 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.

Financial support was obtained from Hartmann's Foundation, the Danish Medical Research Council, and the Danish Medical Association Research Fund.

We conclude that MEPs from the external anal sphincter are adequate for serological screening.

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

<table>
<thead>
<tr>
<th>Cortical stimulation</th>
<th>Sacral stimulation</th>
</tr>
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<tbody>
<tr>
<td><strong>Latency (ms)</strong></td>
<td><strong>Amplitude (mV)</strong></td>
</tr>
<tr>
<td>ADPSP (n=11)</td>
<td></td>
</tr>
<tr>
<td>28.0 (24.2–53.2)</td>
<td>0.04 (0.02–0.18)</td>
</tr>
<tr>
<td>ADPSP (without LUTS and RUI) (n=5)</td>
<td>26.0 (24.2–28.0)</td>
</tr>
<tr>
<td>33.6 (26.5–53.2)</td>
<td>0.03 (0.02–0.05)</td>
</tr>
<tr>
<td>Controls (n=12)</td>
<td></td>
</tr>
<tr>
<td>22.0 (20.9–25.5)</td>
<td>0.16 (0.04–0.42)</td>
</tr>
</tbody>
</table>

LUTS=Lower urinary tract symptoms; RUI=rectal urgency/urge incontinence; CL=cortical latency; CMAP=compound muscle action potential.
Our current practice, based on the results of this audit and the literature available, is to check the renal function of all patients before IVlg 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 IVlg treatment and are currently receiving low sucrose or no sucrose (Octagam(Octopharma)) IVlg formulations. Patients with more seriously impaired renal function are not being considered for IVlg therapy; alternative modes of treatment—for example, plasmapheresis—could be considered for this subgroup. Haematological function is also checked before IVlg therapy, if normal, no further monitoring is carried out during or after IVlg treatment. If there is evidence of mild leucopenia, neutropenia, or thrombocytopenia before IVlg, the full blood count is monitored on a daily basis during treatment and once more 5 days after treatment. Patients with more severe blood derangement (platelets<100×10⁹, neutrophil count<1×10⁹, and leucocyte count>2×10⁹) are not being considered for IVlg therapy and again alternative modes of therapy would be considered.

A consensus statement on the recommended duration of treatment course (1–2 days) was adopted, and the requirement for blood monitoring during IVlg 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 IVlg justify a call for such a study.

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

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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 10 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 palidotomy and the control groups were found for age (years (SD) palidotomy group 56.3 (6.9), control group 59.3 (7.9)), sex (pallidotomy group 50% women, control group: 50%), years of education (years (SD) palidotomy 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

Table 1  Neurological and neuropsychological findings

<table>
<thead>
<tr>
<th>Pallidotomy group</th>
<th>Initial evaluation</th>
<th>Follow up evaluation</th>
<th>Control group</th>
<th>Initial evaluation</th>
<th>Follow up evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini mental state examination</td>
<td>26.4 (3.4)</td>
<td>25.3 (3.3)</td>
<td>26.3 (3.3)</td>
<td>27.5 (2.2)</td>
<td></td>
</tr>
<tr>
<td>UPDRS motor score</td>
<td>15.4 (7.8)</td>
<td>10.8 (5.3)</td>
<td>18.8 (15.8)</td>
<td>15.1 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Levodopa dosage</td>
<td>785 (379)</td>
<td>775 (429)</td>
<td>390 (346)</td>
<td>890 (711)</td>
<td></td>
</tr>
<tr>
<td>Raven's progressive matrices</td>
<td>39.9 (33.8)</td>
<td>53.9 (36.1)</td>
<td>59.8 (36.5)</td>
<td>62.2 (34.3)</td>
<td></td>
</tr>
<tr>
<td>Wisconsin card sorting test</td>
<td>5.7 (2.1)</td>
<td>4.0 (2.5)</td>
<td>4.0 (1.9)</td>
<td>4.0 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>33.0 (8.9)</td>
<td>37.3 (6.4)</td>
<td>38.8 (9.8)</td>
<td>41.0 (13.4)</td>
<td></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 (15.3)</td>
<td></td>
</tr>
<tr>
<td>Buschke delayed</td>
<td>3.3 (3.1)</td>
<td>5.5 (3.0)</td>
<td>6.8 (3.0)</td>
<td>5.8 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Benton visual retention test</td>
<td>5.7 (3.0)</td>
<td>7.1 (2.6)</td>
<td>7.7 (2.0)</td>
<td>7.5 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Digits forward</td>
<td>5.3 (0.8)</td>
<td>5.0 (1.0)</td>
<td>5.7 (1.1)</td>
<td>5.6 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Digits backward</td>
<td>3.6 (0.8)</td>
<td>3.8 (0.8)</td>
<td>4.2 (1.0)</td>
<td>4.4 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Perdue pegboard test*</td>
<td>14.0 (5.5)</td>
<td>17.9 (2.6)</td>
<td>19.3 (5.5)</td>
<td>18.9 (6.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means (SD).

*P<0.05. *P<0.01.
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 neuropsychological variables comparing patients with either a left (n=7) or right (n=9) pallidotomy showed no significant group effect ($F(1,7)=0.95; NS$), time effect ($F(1,7)=1.03; NS$), or group*time interaction ($F(8,56)=0.12; NS$).

A repeated measures MANOVA for the neuropsychological 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 deficits 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 cannot rule out that the 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 who had 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 in Parkinson’s disease does not produce significant cognitive deficits, given that some case reports described various intellectual problems after spontaneous pallidal lesions. Firstly, most lesion studies included patients with bilateral lesions, whereas pallidotomy is usually performed on one side only. The few reports of bilateral pallidotomy in Parkinson’s disease described important cognitive sequelae in some of the patients. Secondly, the neuropsychological sequelae can be small and localised, whereas spontaneous pallidal lesion sizes are usually larger and often involve white matter tracts next to the pallidum. Finally, some of our 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 Perez Companc. We thank Fred Bylsma PhD for his useful suggestions.

**Table 1 Schedule, place, and amount of botulinum toxin injection**

<table>
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Injected muscle</td>
<td>July</td>
<td>October</td>
</tr>
<tr>
<td>Trapezium</td>
<td>50 IU BOTOX&lt;sup&gt;*&lt;/sup&gt; (each trapezium)</td>
<td>30 IU BOTOX&lt;sup&gt;*&lt;/sup&gt; (right trapezium)</td>
<td>30 IU BOTOX&lt;sup&gt;*&lt;/sup&gt; (each trapezium)</td>
</tr>
<tr>
<td>Esternocleidomastoid (ECM)</td>
<td>30 IU BOTOX&lt;sup&gt;*&lt;/sup&gt; (each ECM)</td>
<td>30 IU BOTOX&lt;sup&gt;*&lt;/sup&gt; (each ECM)</td>
<td>20 IU BOTOX&lt;sup&gt;*&lt;/sup&gt; (each side)</td>
</tr>
<tr>
<td>Paracervical musculature</td>
<td>20 IU BOTOX&lt;sup&gt;*&lt;/sup&gt; (each side)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The patient received 50 IU BOTOX<sup>*</sup> (Allergan) in three different locations of each trapezius on 17 July 1996; on 24 October 1996, 30 IU BOTOX were administered in each esternocleidomastoid and 30 IU in right trapezius; on 22 January 1997 30 IU BOTOX were given in each esternocleidomastoid 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 musculature (total 80 IU); on 15 January 1998 10 IU BOTOX were given in each trapezius and 30 IU in paracervical musculature bilaterally.
the patient (fig 1). The radiological and functional measurements confirmed this assessment: in January 1996 the distance from chin to sternum was 10 cm in maximum neck flexion, in December 1997 this distance was 3 cm and in June 1999 the patient was able to touch his sternum with his chin. In March 1999 the patient developed myocarditis, with acute thoracic pain two weeks after a sore throat, increased creatine kinase concentrations, and electrocardiographic changes, with good recovery in 1 week. An echocardiogram performed 3 months later was normal and serology for Coxsackie virus was positive.

BOTOX is the trade mark of the commercialised type A toxin of Clostridium botulinum; BOTOX causes muscle paralysis by acting at nerve endings and blocking presynaptically the release of quanta of acetylcholine; this muscular paralysis is reversible and can ameliorate symptoms in patients with muscle spasms appearing as a manifestation of multiple neurological disturbances, including myopathies. In some situations this amelioration may become last long, and patients will not require further injections. The American Academy of Neurology recommends its therapeutic use in blepharospasm as a primary form of therapy; its use is accepted in cervical dystonia, adductor spasmodic dysphonia, jaw closing dystonia, and hypertelorism of hemifacial spasm; its use is considered promising in jaw opening and deviation dystonia, adductor spasmodic dysphonia, and in other focal dystonias.

The origin of spine stiffness in rigid spine syndrome is not well understood. Shortening of paraspinal ligaments or shortening of muscle fibres due to myofibril disorganisation have been invoked as possible origins of stiffness; weakness of neck flexors 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 developing 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 Graells for linguistic assessment.

**“Hot cross bun” sign in a patient with parkinsonism secondary to presumed vasculitis**

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 thepons (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 a 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 ataxia in all 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 flox.

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 21.6 g/l (with a polyclonal pattern on electrophoresis), a positive rheumatoid factor titre (>1:320), a positive speckled ANA titre (>1:640), and positive anti-Ro antibodies (33 units). Schärmer’s test, thyroid function tests, copper levels, 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 hyperintensity within thepons (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 tract. Wallerian degeneration of the pons makes 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 people involved with CMT. It is well written and excellently presented and provides a range of information that the intended audience will find invaluable.

The book is divided into three main sections. The first section deals with genetic and medical issues. The known genetic variants of the disease are well described and accurate except for one mistake stating that the gene duplication that causes CMT1a is on chromosome 22 when it is actually on chromosome 17. I thought the section covering CMT inheritance was particularly well presented and illustrated using simple diagrams to explain the various inheritance mechanisms. There was also a very useful glossary of scientific and medical terms in this section.

The second section deals with living with CMT. This covers many important areas for the patient including coming to terms with the diagnosis, care of the feet, pain control, and secondary complications. Foot deformities and their surgical correction were particularly well covered.

The third section deals with practical issues including finding work, having a baby, driving, and CMT and aids to daily living. This section is particularly useful in providing contact details for many different organisations who will help patients. All three sections are supported by informative appendices.

This book is an excellent patient orientated 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 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, interpersonal 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 Pettit, Polhala, 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 Vitaro 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. "service providers will pay heed to this message."

"An important role of rehabilitation is one of the most potent factors that can promote the transition of those with traumatic brain injury to independent fulfilling lives."

The main take home message is captured in chapter 12—namely that “Brain injury rehabilitation is best conducted in services dedicated to those with acquired brain injury, for the majority of whom personality changes and cognitive impairments are the primary disabilities”. Given firstly, the low priority of rehabilitation for people with cognitive and personality changes after acquired brain injury; secondly, the fact that many with traumatic brain injury are sent to any ward that has an empty bed; and thirdly, that many are under the care of orthopaedic surgeons or rheumatologists rather than specialists in brain injury, it is to be hoped that neurologists, neurosurgeons, psychiatrists, and health service providers will pay heed to this message.


This book is the result of the author’s long standing interest in and contributions to benign seizures, 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.

"Benign epilepsy, perhaps more than many other medical disorders, 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 may 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 in such a way that there is 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 difficulties, 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 predicament 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, passing 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 no doubt enhance the library of any person with an interest in measuring outcome in epilepsy.

CORRECTION

Corrections to Appendix 2 are noted here:

1. "Dr Panayiotopoulos puts forward the view that the benign childhood partial seizure disorder 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."

2. "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, passing almost every aspect of this domain."

3. "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 no doubt enhance the library of any person with an interest in measuring outcome in epilepsy."

4. "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."

5. "Epilepsy, perhaps more than many other medical disorders, 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 may 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 in such a way that there is 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 difficulties, which potentially threaten the quality of life of people with epilepsy."

6. "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 predicament and vital capacity to live independent fulfilling lives are important considerations."

7. "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, passing 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 no doubt enhance the library of any person with an interest in measuring outcome in epilepsy."

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Very early onset Alzheimer's disease with spastic paraparesis associated with a novel presenilin 1 mutation (Phe237Ile)

N SODEYAMA, T IWATA, K ISHIKAWA, H MIZUSAWA, M YAMADA, Y ITOH, E OTOMO, M MATSUSHITA and Y KOMATSUZAKI

J Neurol Neurosurg Psychiatry 2001 71: 556-557
doi: 10.1136/jnnp.71.4.556