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 over 60 mutations have been found so far. There are phenotypic variations among mutations on PS1. Three PS1 mutations, deletion of exon 9 with and without splice acceptor site mutation, and Arg278Thr have been reported to be associated with Alzheimer’s disease with spastic paraparesis. 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 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. 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). 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’-GGAGATTGGAAGAGCTGGC AATG-3’).

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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.
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 9. Phe237Ile 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 mutation might be related to 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 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.


Thirdly, three mutations of PS1, loss of exon 9, and without mutation of splice acceptor site mutation, and Arg287Thr are associated with Alzheimer’s disease with spastic paraparesis. 

Forthly, PET 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. 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 Welfare, Japan and Grants in Aid for Scientific Research (to HM and MY) from the Ministry of Education, Science, Sports, and Culture, Japan.
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 pathogenesis, such as hyperphosphorylated tau, synapse specific proteins (for example, synaptophysin, or APP isoforms for example, 

\[
\text{beta-amyloid (1-42) (filled circle) or healthy control (open square). Filled circles=Alzheimer's disease; open squares=healthy controls.}
\]

\[p=0.002\]. There was also a significant difference in CSF-NSE (7.4 (2.7) ng/l; \(p=0.014\)). By contrast, there were no significant differences in 

\[A\beta_{42},\] 

\[\text{A}\beta_{40},\] 

\[\text{NSE},\] 

\[\text{tau}\] 

p\(=0.097\).)

\[18\%\] of cases.

\[A\beta_{42}\] in patients with Alzheimer’s disease compared with controls (7.48 (297) ng/ml; \(p<0.0001\)) and a slight but significant decrease in CSF S-100B (1.8 (0.9) ng/ml; \(p=0.014\)). By contrast, there were no significant differences in 

\[42\) resulted in any further increase in head lice treatments, 

\[1.8\) of experimental organisms, such as in the figure above. Filled circles=Alzheimer’s disease; open squares=healthy controls.

\[p=0.057\) of SF2, and CSF GFAP (860 (297) ng/l; \(p=0.097\)).

\[\text{neurofilament protein in CSF.}\]

\[144–55\). The distribution of \(A\beta_{42}\) and \(A\beta_{40}\) concentrations (fig 1). The NSE and S-100B 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 discrimination of 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-100B) 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 pathogenesis, such as hyperphosphorylated tau, synapse specific proteins (for example, synaptophysin, or APP isoforms for example, \(\beta\)-secretase cleaved APP), may have a larger impact 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; Stiftelsen for Gamla Tjänarinnor, Stockholm, Sweden; Tore Nilssons Fond for Medicinsk Forskning, Stockholm, Sweden; Norrbottens Län Landstings FoU Fund, Sweden; Svenska Lakaresällskapet, Stockholm, Sweden; and Ake Wibergs Stiftelse, Stockholm, Sweden. We are grateful to Mrs Christina Sjödin and Mrs. Maria Ländby for skilful technical assistance.

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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, 1 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, 2 but 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 \(\alpha\)-1-antitrypsin (\(A\alpha\)) gene family of genes are associated with incidence of vCJD and was based on the hypothesis that exposure to \(\alpha\)-toxins, widely used as insecticides in the United Kingdom, was causally related to the prion disease (PrP) epidemic. 3 Previous work suggested a major role in the detoxification of many organophosphate pesticides: PON1 allelic variants confer fast or slow abilities to detoxify these xenobiotics. 4 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 prescription to heart medications. 5 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 flies, upregulates the cell surface levels of normal prion protein in human neuronal cells; 6 high levels of PrP expression are themselves known to be associated with increased ease of transmission of prion diseases. 7 Although it has been hypothesised 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, 147, and 95 controls 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, 1.

Statistical analysis of the data was performed using the Pearson’s \(\chi^2\) test (\(p<0.05\)). The distribution of \(\alpha\)-1-antitrypsin (\(A\alpha\)) genotype 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 frequencies of alleles \(L(\text{Leu})\) and \(M(\text{Met})\) at codon 54 of PON1 were respectively 0.672 and 0.328 in controls (\(n=95\), 0.654 and 0.346 in vCJD, 0.684 and 0.316 in sporadic CJD, and 0.737 and 0.269 in neurological controls). The frequencies for alleles \(G(\text{Gln})\) and \(B(\text{Arg})\) at codon 192 of PON1 were respectively 0.726 and 0.274 (\(n=117\)) in the controls, 0.731 and 0.269 in vCJD, 0.737 and 0.263 in sporadic CJD, and 0.700 and 0.300 in neurological controls. Finally, the frequencies for alleles \(S(\text{Ser})\) and \(C(\text{Cys})\) at codon 311 of PON2 were respectively 0.747 and 0.226 in controls (\(n=95\), 0.769 and 0.231 in vCJD, 0.763 and 0.237 in sporadic CJD, and
There were no significant differences between the cases and controls.

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>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>n</td>
<td>n</td>
<td>n</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/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>
</tr>
<tr>
<td>Codon 192:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/A</td>
<td>63 (53.8)</td>
<td>5 (50)</td>
<td>10 (52.6)</td>
<td>14 (53.8)</td>
</tr>
<tr>
<td>AB</td>
<td>44 (37.6)</td>
<td>4 (40)</td>
<td>8 (42.1)</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>BB</td>
<td>10 (8.5)</td>
<td>1 (10)</td>
<td>1 (5.3)</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>n</td>
<td>117</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/Arg</td>
<td>0.726</td>
<td>0.700</td>
<td>0.737</td>
<td>0.731</td>
</tr>
<tr>
<td>B/Arg</td>
<td>0.274</td>
<td>0.300</td>
<td>0.263</td>
<td>0.269</td>
</tr>
<tr>
<td>Codon 311:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S/S</td>
<td>57 (60)</td>
<td>5 (50)</td>
<td>12 (63.2)</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td>C/S</td>
<td>33 (34.7)</td>
<td>4 (40)</td>
<td>5 (26.3)</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>C/C</td>
<td>5 (5.3)</td>
<td>1 (10)</td>
<td>2 (10.5)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>n</td>
<td>95</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S/Ser</td>
<td>0.774</td>
<td>0.700</td>
<td>0.763</td>
<td>0.769</td>
</tr>
<tr>
<td>C/Cys</td>
<td>0.226</td>
<td>0.300</td>
<td>0.237</td>
<td>0.231</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.

The patient was able to perform voluntary movement using the bilateral rectus abdominis, obliquus externus abdominis, and obliquus internus abdominis muscles, but she was not able to perform voluntary movement using the hip flexors, which are under the control of L2, and lower level muscles. An EEG, recorded at rest, and MRI of the brain showed no significant abnormalities. In addition, the patient had no history of seizure.

Treatment was by means of drugs (clonazepam and haloperidol), transcutaneous electrical nerve stimulation of the lower intercostal nerve, which innervates the obliquus externus abdominis, and a lumbar extradural nerve block at the level of T10–12. However, these treatments had no effect on the involuntary movement.

A trial study of rTMS was designed to investigate whether it could improve the involuntary movement of the trunk and lower limbs. The study was performed using a commercially available stimulator (MagStim 200) and a round coil (13 cm in diameter) according to the following protocol: 50 stimuli of 0.25-Hz rTMS at the intensity of 110% of the motor threshold were delivered to the right prefrontal cortex in the clockwise direction of the electrical current of the coil. In succession, 50 stimuli of 0.25-Hz rTMS at the intensity of 110% of the motor threshold were delivered to the left prefrontal cortex in the clockwise direction of the electrical current in the same coil. One session consisting of these 100 stimuli was delivered once a day and was repeated for 5 consecutive days.

The motor threshold was assessed by application of a single stimulation with inter-stimulus interval of more than 10 seconds to the presumed motor area for activation of the contralateral abductor pollicis brevis muscle. 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 an 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 stimulations 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 oblique 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 threshold, although an EEG was not recorded. For the purpose of avoiding skin burn, radial notched electrodes were used while recording the EEG.

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 reversed to a 10–20 Hz wave (fig 1). When rTMS to the right
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The 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.

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 centrotemporal 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 hypsarrhythmia. 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 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 behaviour 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 slow alternating tongue 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 pre-existing pathology. Severe language impairment at 2.5 years might suggest a variant of existing pathology. Severe language impairments with infantile spasms: late age of onset, for example, “zip”.

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obtained in upper and lower limb muscles are presented elsewhere. The results are presented as median (range), and the distributions were compared by the Kruskal-Wallis test. The level of significance was set to 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. The CL and CMCT are shown in table 1.

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 to the external anal sphincter may be a method to be used as a part of the evaluation of patients with supernuclear lesions and sphincter symptoms.

In neuropsychological 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 supernuclear lesions and RUI.

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

The conditions treated included Guillain- Barre syndrome, chronic inflammatory demyelinating polyneuropathy, and dermatomyositis. 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 concentrations) within 6 months normal. Eight patients had indications of possible renal dysfunction (based on one or more abnormal blood urea and creatinine concentrations) within 6 months.

Various complications have been reported in the literature in association with IVlg therapy. These include headache, nausea, fever, rash, aches in the chest or limbs, anaphylaxis especially in association with IgA deficiency, leukopenia, neutropenia, autoimmune haemolysis, renal failure, thrombocytopenia, aseptic meningitis, and transmission of viral infections—for example, hepatitis C.1 The therapeutic dose of IVlg in the treatment of neurological disease has been empirically set at 0.4 g/kg, conventionally divided into several 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.

Despite the widespread use of IVlg 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 IVlg, nor on the merits of shorter infusion periods of IVlg. 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 IVlg 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- Barre syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, polymyositis, Lambert-Eaton myasthenic syndrome, stiff man syndrome, and Rasmussen’s encephalitis.1

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

Intravenous immunoglobulin (IVlg) is widely used in the treatment of some neurological conditions thought to have an underlying immune basis. Controlled studies of IVlg have demonstrated benefit in Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and dermatomyositis. Treatment with IVlg 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.

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

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>Latency (ms)</th>
<th>Amplitude (mV)</th>
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</thead>
<tbody>
<tr>
<td>ADPSP (n=11)</td>
<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>
<td>0.07 (0.03–0.18)</td>
</tr>
<tr>
<td>ADPSP (without LUTS and RUI) (n=6)</td>
<td>33.6 (26.5–53.2)</td>
<td>0.03 (0.02–0.05)</td>
</tr>
<tr>
<td>Controls (n=12)</td>
<td>43.0 (22.0–29.5)</td>
<td>0.16 (0.04–0.42)</td>
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<table>
<thead>
<tr>
<th>Sacral stimulation</th>
<th>Latency (ms)</th>
<th>Amplitude (mV)</th>
<th>CMCT (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADPSP (n=11)</td>
<td>5.2 (4.0–7.5)</td>
<td>0.15 (0.04–0.39)</td>
<td>22.8 (18.4–48.0)</td>
</tr>
<tr>
<td>ADPSP (without LUTS and RUI) (n=5)</td>
<td>5.8 (4.2–7.5)</td>
<td>0.15 (0.04–0.34)</td>
<td>20.7 (18.4–21.8)</td>
</tr>
<tr>
<td>ADPSP (without LUTS and RUI) (n=6)</td>
<td>5.1 (4.0–5.0)</td>
<td>0.18 (0.08–0.39)</td>
<td>29.0 (22.8–48.0)</td>
</tr>
<tr>
<td>Controls (n=12)</td>
<td>4.7 (3.0–7.8)</td>
<td>0.23 (0.02–0.59)</td>
<td>19.6 (16.5–23.5)</td>
</tr>
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</table>

LUTS=Lower urinary tract symptoms; RUI=rectal urgency/urge incontinence; CL=cortical latency; CMAP=compound muscle action potential. ADPSP with LUTS/RUI v ADPSP without LUTS/RUI: CL p=0.02; CMAP amplitude p=0.03; CMCT p=0.01. ADPSP with LUTS/RUI v control persons: CL p=0.002; CMAP amplitude p=0.01; CMCT p=0.001.

Our current practice, based on the results of this audit and the literature available, is to check the renal function of all patients before IV Ig 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 IV Ig treatment and are currently receiving low sucrose or no sucrose (Octogam(Octopharma)) IV Ig formulations. Patients with more seriously impaired renal function are not being considered for IV Ig therapy; alternative modes of treatment—for example, plasmapheresis—could be considered for this subgroup. Haematological function is also checked before IV Ig therapy; if normal, no further monitoring is carried out during or after IV Ig treatment. It was noted that there was no consensus on the level of leucopenia, neutropenia, or thrombocytopenia before IV Ig, 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 (platelet<100×10⁹/l, neutrophil count<1×10⁹/l, and leucocyte count<2×10⁹/l) are not being considered for IV Ig therapy and again alternative modes of therapy would be considered.

A consent statement on the recommended duration of treatment course (1–2 days v 5 days) and the requirement for blood monitoring during IV Ig 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 IV Ig justify a call for such a study.

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

<table>
<thead>
<tr>
<th>Table 1 Neurological and neuropsychological findings</th>
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<tr>
<td><strong>Pallidotomy group</strong></td>
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<tr>
<td><strong>Initial evaluation</strong></td>
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<tr>
<td><strong>Mini mental state examination</strong></td>
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<tr>
<td><strong>UPDRS motor score</strong></td>
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<td><strong>Levodopa dosage</strong></td>
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<td><strong>Raven’s progressive matrices</strong></td>
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<td><strong>Wisconsin card sorting test</strong></td>
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<td><strong>Verbal fluency</strong></td>
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<tr>
<td><strong>Buschke total recall</strong></td>
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<td><strong>Buschke delayed</strong></td>
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<td><strong>Benton visual retention test</strong></td>
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<tr>
<td><strong>Digit forward</strong></td>
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<tr>
<td><strong>Digit backwards</strong></td>
</tr>
<tr>
<td><strong>Perdue pegboard test</strong></td>
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</table>

Values are means (SD).
*P* (1,28)=88.84, p<0.01.
The patient received 50 IU BOTOX® (Allergan) in three divided in each esternocleidomastoid and 30 IU in right trapezium; on 22 January 1997 30 IU BOTOX were given in each esternocleidomastoid and trapezium; on 21 January 1998 10 IU BOTOX were given in each trapezium and 30 IU in paracervical musculature bilaterally.

May 1997 20 IU BOTOX were given in each trapezium; on 25 September 1997 40 IU BOTOX were given in each trapezium and bilateral paracervical musculature.

Response to botulinum toxin in a case of rigid spine syndrome

First described by Dubowitz in 1965, 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.1 Recently, a local locus for this syndrome has been identified on chromosome 1p.1 In laboratory studies serum creatine kinase concentrations can be raised. Electromyographic studies of paracervical musculature, trapezium, 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 disproportions; 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 muscular dystrophy, primary myotonia congenita, myotonia dystrophica from Emery-Dreifuss muscular dystrophy and from early onset ankylosing spondylitis, as prognostics are different. The rigid spine sign has also been reported in Betzhalmyopathies and muscular dystrophies 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.2 Here we report a good response to botulinum toxin type A (BOTOX) treatment in a young man with rigid spine syndrome.

A 15 year old boy born at term, with congenital hypospadias and normal psychomotor development, was being studied by an endocrinologist because of short stature (mother's stature 145 cm, father's stature 169 cm) the noticed progressive decrease in height, neck flexion limitation and referred him 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 mother 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 marked postural kyphosis and contracture of neck extensors severely limiting movement in the anterior and lateral senses; hip flexion was severely affected (below 30º); no pain was produced by sacral manoeuvres. Radiological examination of the cervicothoracic spine showed scoliosis without vertebral malformations, 65º cervical lordosis involving C2 to C7, and a 55º thoracic kyphosis involving T3 to T12. Routine blood testing showed no abnormalities and creatine kinase concentrations were normal; autonomic symptoms 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 muscular atrophy, and right quadriceps) with

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

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<tbody>
<tr>
<td>Injected muscle</td>
<td>July</td>
<td>October</td>
<td>January</td>
</tr>
<tr>
<td>Trapezium</td>
<td>50 UI BOTOX*</td>
<td>(each trapezium)</td>
<td>30 UI BOTOX*</td>
</tr>
<tr>
<td>Ecternocleido mastoid (ECM)</td>
<td>30 UI BOTOX*</td>
<td>(each ECM)</td>
<td>30 UI BOTOX*</td>
</tr>
</tbody>
</table>

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 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.

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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 myocaraditis, 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 typeA toxin of Clostridium botulinum; BOTOX causes muscle paralysis by acting at nerve endings and blocking presynaptically the release of quanta of acetylcholine; this muscle 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 long lasting, 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 hyperkinesis of hemifacial spasm; its use is considered promising in jaw opening and deviation dystonia, abductor 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 myofibrillar disorganisation have been invoked as possible origins of stiffness; weakness of neck muscles can make this group of muscles incapable of countering 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 Grachts for linguistic assessment.

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 demonstrated a non-enhancing swelling of the pons (fig 1 A). She had 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 limb 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 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 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). Schirmer’s test, thyroid function tests, copper, zinc, 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 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 parkinsonism 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.\textsuperscript{1} The aetiological and CSF findings together with initial pontine swelling suggested plausible vasculitis, a recognised cause of parkinsonism.\textsuperscript{2} Wallerian degeneration secondary to vasculitis infarction results in hyperintensity on T2 weighted MRI.\textsuperscript{3} 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.

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 disease, 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 oriented 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 a 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 standpoints.

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, Pohlaha, 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 biocultural influences, in which he conveys a sense that is available to the 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 standpoints.

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This short book describes the fascinating recovery and remarkable neurocognitive compensation of Nico, a little boy who at the

MOIRA DOOLAN


This short book describes the fascinating recovery and remarkable neurocognitive compensation of Nico, a little boy who at the

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Neurobehavioural disability and social handicap following traumatic brain injury. Although such cases are not now rare, the emphasis on how the neuropsychology of hemisphericity can be used to inform education theory makes for an intriguing and readable book—part case history, part speculation, and from time to time—part educational manifesto. Throughout, however Battro manages to communicate the intricacies of brain surgery, neuronal architecture, developmental psychology, and functional imaging in such a way as to render the take-home message for an “epigenetic neurocognitive approach” both relevant and understandable. Supporting his belief that these functions were mediated by brain amounts to is a “new brain”, Battro makes full use of the power of detailed single case observations to illustrate how Nico’s abilities (musical motor and attention) have all developed normally despite the traditional belief that these functions were mediated by the right hemisphere. The only major behavioural impairment that Nico retained was poor constructional and handwriting skills, a handicap that Battro successfully succeeds in compensating by providing a computerised “information prosthesis”.

Although some may take issue with some of the generalisations and speculations outlined—overall the book revisits important issues relevant to neuropsychology that deserve consideration by clinicians and neuroscientists alike.

PETER HALLIGAN


This book is one of a series entitled Brain damage, behaviour and cognition. It comprises 13 chapters in three parts. The first part covers “the nature and impact of neurobehavioural disability”; the second addresses “rehabilitating neurobehavioural disability” and the final one is concerned with “models of service delivery”. Although the contributors come from the United Kingdom, North America, and Australia, the focus (to a large extent) is on British rehabilitation.

To me, the best section, overall, was part three, “models of service delivery”. I found chapter 12 by McMillan and Oddy “service provision for social disability and handicap after acquired brain injury” helpful and informative and full of common sense. The previous chapter by Giles “the effectiveness of neurorehabilitation” was also useful, not least because of the many outcome studies referred to. Of the treatment chapters, chapter 8 by Alderman and chapter 9 by Evans on “challenging behaviours” and “the dysexecutive syndrome” are well worth reading. Parts of the book came over as either rather bland or less useful for readers of this Journal.

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.

BARBARA A WILSON


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

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 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 disabilities, 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 no 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 cytogenic abnormality.”

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