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.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 hyperreactive 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 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. Somatosensory evoked potential was normal. An EEG showed generalised slowing with background theta. Somatosensory evoked potential was normal. An EEG showed generalised slowing with background theta. Somatosensory evoked potential was normal. An EEG showed generalised slowing with background theta. Somatosensory evoked potential was normal. An EEG showed generalised slowing with background theta. Somatosensory evoked potential was normal. An EEG showed generalised slowing with background theta. Somatosensory evoked potential was normal. An EEG showed generalised slowing with background theta. Somatosensory evoked potential was normal. An EEG showed generalised slowing with background theta. Somatosensory evoked potential was normal. 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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.

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.

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In agreement with previous findings, increased CSF tau and decreased CSF A
did not discriminate 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%).

The discriminant regressor was Alzheimer’s disease (filled circles) or healthy control (open square). Highest correlation was found for Aβ42 with Alzheimer’s disease. Tau and NFL also correlated with Alzheimer’s disease; however, including some structure not related to the disease (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 all CSF protein concentrations (index protein assessment as in the figure above). Filled circles=Alzheimer’s disease; open squares=healthy controls.

The combination of CSF tau and CSF Aβ42 concentrations was found to be a sensitive test for Alzheimer’s disease (91.4%) and specificity for 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 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 S-100β 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%).

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 such as hyperphosphorylated tau, synapse specific proteins (for example, rab5a, synaptotagmin), or APP isoforms (for example, β-secretase or β-secretase cleaved APP), may have a larger potential as CSF biomarkers for Alzheimer’s disease.

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

This study aimed to establish whether polymorphisms in the paraoxonase (PON) 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 vCJD. Previous studies have shown a major role in the detoxification of many organophosphate pesticides; PON1 allele 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 predisposition 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 PON1 expression. This suggests that PON1 may play a role in detoxifying xenobiotics, such as OPs, and that this polymorphism may be one that is 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, 117, and 95 normal persons, 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, UK.

Statistical analysis of the data was performed using the Pearson’s χ² test (p<0.05). The distribution of PON1 and PON2 genotypes and allele frequencies in patients and controls is shown in table 1. All genotype frequencies did not deviate significantly from the predicted Hardy-Weinberg equilibrium (data not shown). The frequencies of allele L(Leu) and M(Met) at codon 54 of PON1 were respectively 0.672 and 0.328 in the control population (n=93), 0.654 and 0.346 in vCJD, 0.684 and 0.316 in sporadic CJD, and 0.765 and 0.235 in neurological controls. The frequencies of allele A(Gln) and B(Arg) at codon 192 of PON1 were respectively 0.726 and 0.274 (n=117) in the control population, 0.731 and 0.269 in vCJD, 0.737 and 0.263 in sporadic CJD, and 0.765 and 0.235 in neurological controls. Finally, the frequencies for alleles S(Ser) and C(Cys) at codon 311 of PON 2 were respectively 0.774 and 0.226 in controls (n=95), 0.769 and 0.231 in vCJD, 0.763 and 0.237 in sporadic CJD, and
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 any of the PON polymorphisms studied and 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 in 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 area1 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 on C4 after the 4th stimulation of rTMS to the right prefrontal cortex in the clockwise direction of the electrical current and 6 seconds later and reverted to an 8–10 Hz slow wave (fig 1). When rTMS to the right frontal cortex was applied using a stimulus intensity of 80% of the motor threshold as determined by magnetic stimulation of the left prefrontal cortex, the patient showed a slow wave after the 4th stimulation of rTMS to the right prefrontal cortex. The slow wave disappeared at least 6 seconds later and reverted to an 8–10 Hz slow wave (fig 1). When rTMS to the right

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>PON1:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codon 54</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>10</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>n</td>
<td>93</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L/L(eve)</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>PON2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codon 192</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</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></td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A(Gln)</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>PON2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codon 311</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SS</td>
<td>57 (60)</td>
<td>5 (50)</td>
<td>12 (63.2)</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td>CS</td>
<td>33 (34.7)</td>
<td>4 (40)</td>
<td>5 (26.3)</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>CC</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></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.

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

Transcranial magnetic stimulation (TMS) has come to be widely used to evaluate the CNS since the first report on the use of TMS in humans by Barker et al in 1985. Depending on the frequency, intensity, and duration of stimulation, trains of repetitive TMS (rTMS) can transiently block or inhibit the function of a cortical region. It has been suggested that rTMS has therapeutic potential for the treatment of Parkinson’s disease1 and psychiatric disorders. To apply rTMS as a clinical tool, an evaluation of the safety margins during the stimulation is required.

A 56 year old woman was admitted to Hokkaido University Medical Hospital on 6 October 1999 for treatment of involuntary movement of the trunk and lower limbs that had persisted for 8 years. In 1991, the patient had a spinal cord injury at thoracic and lumbal levels. The occurrence of the involuntary movement was irregular and was not precipitated by any obvious conditions. 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 in 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 area1 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 on C4 after the 4th stimulation of rTMS 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 using F3, F4, C3, and C4, according to the International 10–20 system, in addition to monitoring MEPs on the bilateral obliquus externus abdominis muscles. Conventional EEGs recorded at rest before and after the rTMS trial did not show any abnormalities. Seizure was not seen during the measurement of motor 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 reverted to a 8–10 Hz wave (fig 1). When rTMS to the right
prefrontal cortex was restarted, a slowing wave of the EEG recurred and lasted longer after the 4th stimulation. This change did not occur during rTMS to the left prefrontal cortex. The recurring slow wave began and disappeared in the same manner. We could not consider 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.

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 centrencephalomalacia and hypsarrhythmia. ACTH (10 units daily and 40 units daily from 10–12 months) stopped the spasms after 2 weeks. Electroencephalography, CT, metabolic investigations, electrotetrography, and visually evoked potentials were normal. CMV antibodies were present in blood, and virus in the urine.

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

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

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

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

A Griffiths assessment at 3.10 years showed significant recovery; hearing and speech 3.8 years; performance 3.6 years;
that age. He transferred from special to mainstream education. Coordination problems continued.

He made good academic progress but with behavior 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, toilet training, and in using a knife and fork. Walking and running were abnormal and he could not use a bicycle. He showed abnormal 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, this child with an otherwise typical presentation, and surgical evidence supports this idea.

The report supports the hypothesis that epileptic syndromes—for example, language impairments with epilepsy—are described, and transient loss of visual function, but not prolonged visual agnosia with infantile spasms. Although subclinical seizures in sleep seem to have been a pervasive effect of infantile spasms. Although subclinical seizures in sleep may indicate earlier cortical storing of information, it is highly probable that in the tight connection with infantile spasms, sometimes painful, of the jaw, legs, and abdomen. Vocalisations were either unintelligible and/or repeated words—for example, “zip”.

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 (ADPSP) linked to chromosome 2p have lower urinary tract symptoms (LUTS) and additionally most of these patients also experience rectal urgency/urge incontinence (RUI) as well as sexual dysfunction.

The direct motor pathway to the external anal sphincter was evaluated 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 ADPSP linked to chromosome 2p and to obtain normative data.

After informed consent was obtained 11 definitely affected patients from six different families with ADPSP 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 20–64) years. Six patients had LUTS and RUI, five of whom previously underwent urodynamical 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 urodynamic findings have been previously described.1 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 Twinpoint 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 13LED, Dantec Medical Inc, Denmark). The position of the electrode was anterosuperior to avoid cancelling of the motor potentials because of bilateral contrac-

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 abductor hallucis (AH) muscle. The motor threshold (MT) was determined as the minimal stimulus intensity applied to the relevant cortical representation evoking a motor response from the 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 space 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) was calculated. The stimulations were performed in at least two 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

![Figure 1](https://example.com/figure1.png)
ADPSP with LUTS/RUI

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

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

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

The CL and the CMC were significantly longer and the amplitude of the 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, CMC, or amplitude of the CMAP compared with the controls. The patients with LUTS and RUI presented significantly longer CL and CMC 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 CMC 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 supranuclear lesions and sphincter symptoms.

In neuropathological studies axonal degeneration was found to be maximal in the terminal portions of the longest descending and ascending tracts. Dorsal root ganglia, posterior roots, and peripheral nerves were normal.  

Axonal degeneration of the corticospinal neurons, however, cannot solely explain the pathogenesis of the disease. Patients without LUTS and RUI presented normal CMCs 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 CMCs and CMAPs compared with controls. These results may in part be related to the pathogenesis of the disease. MEPs from the external anal sphincter can be relatively easily evoked and may be a new useful method in the evaluation of patients with supranuclear lesions and RUI.

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-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, 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, leucopenia, neutropenia, autoimmune haemolyis, renal failure, thrombocytopenia, astasia, aseptic meningitis, and transmission of viral infections—for example, hepatitis C.  

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

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 post-treatment 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-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, and myasthenia gravis. The average age of patients was 51 years (range 22–86 years).

Eight patients had indications of possible renal dysfunction (based on one or more abnormal blood urea and creatinine concentrations) within 6 months normal. Amonalaxination of the corticospinal neurons, however, cannot solely explain the pathogenesis of the disease. Patients without LUTS and RUI presented normal CMCs 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 CMCs and CMAPs compared with controls. These results may in part be related to the pathogenesis of the disease. MEPs from the external anal sphincter can be relatively easily evoked and may be a new useful method in the evaluation of patients with supranuclear lesions and RUI.

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>
<th>Latency (ms)</th>
<th>Amplitude (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADPSP (n=11)</td>
<td>28.0 (24.2–53.2)</td>
<td>0.04 (0.02–0.18)</td>
<td>5.2 (4.0–7.5)</td>
<td>0.15 (0.04–0.39)</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>
<td>5.8 (4.2–7.5)</td>
<td>0.15 (0.04–0.4)</td>
</tr>
<tr>
<td>ADPSP (with LUTS and RUI) (n=6)</td>
<td>33.6 (26.5–53.3)</td>
<td>0.03 (0.02–0.05)</td>
<td>5.1 (4.0–5.2)</td>
<td>0.18 (0.08–0.39)</td>
</tr>
<tr>
<td>Controls (n=12)</td>
<td>24.0 (22.0–29.5)</td>
<td>0.16 (0.04–0.42)</td>
<td>4.7 (3.0–7.8)</td>
<td>0.23 (0.02–0.59)</td>
</tr>
</tbody>
</table>

CMCT (ms) Latency (ms) Amplitude (mV) Latency (ms) Amplitude (mV)

ADPSP with LUTS/RUI: ADPSP without LUTS/RUI: CL: p=0.02; CMAP amplitude p=0.03; CMCT p=0.01.

ADPSP with LUTS/RUI: control persons: CL: p=0.002; CMAP amplitude p=0.01; CMCT p=0.001.

The results are presented as median (range), and the distributions were compared by the Kruskal–Wallis test. The level of significance was set at 0.05.
range 60–120 µM). Other adverse effects noted which did not delay or stop treatment included tachycardia (one patient), fall in haemoglobin (one), persistent pyrexia (one), nausea and vomiting (four), limb or chest pain (four), rigors (two), and headache (two). It should be noted that there was no correlation on the level of leucopenia, neutropenia, raised urea, or creatinine at which treatment was discontinued among the six consultant neurologists at the centre. During a 5 day course, the white cell count was noted to fall below 4×10⁹/l in 12 patients and the neutrophil count to below 2.0×10⁹/l in eight patients. Urea and creatinine concentration only became abnormal in one patient (who developed renal failure requiring haemodialysis) whose renal function was mildly impaired before treatment (sodium 133 mM, potassium 4.6 mM, urea 7.0 mM, and creatinine 138 µM). In all patients with noted haematological derangement secondary to IVIg treatment, subsequent blood monitoring 14 days after stopping treatment showed a return to normal values.

The number of patients who had abnormal blood variables during this retrospective study suggests a need to establish guidelines for monitoring haematological and renal variables during IVIg therapy. Furthermore, given the cost implications of an abortive course of treatment, guidelines for tolerable level of leucopenia, neutropenia, or urea/creatinine derangement during a standard 5 day course of IVIg also needs to be established. It may well be that neutropenia during IVIg treatment is transient and resolvable, as suggested by this study, and if validated, there would be an argument against the need for regular haematological monitoring during IVIg therapy. This argument is supported by the findings of Koffman and colleagues, who retrospectively reviewed the records of 46 patients with neuromuscular disease receiving standard courses of IVIg (Gaminune N (Bayer) 2 g/kg) compared with 23 patients given placebo infusions of dextrose in water. In this study leucopenia, neutropenia, and lymphopenia were noted in a large proportion of patients treated with IVIg. Thus this has significant side effects—for example, infection—resulted and all haematological derangements were transient.

Furthermore, consensus needs to be established on the effect of IVIg formulations and risk of sucrose nephropathy (sucrose is used as a stabiliser in some IVIg preparations). Some previous case reports have suggested a link between the use of high sucrose formulations of IVIg (for example, Sandoglobulin (Novartis)) and subsequent renal failure compared with the use of lower sugar or glycine based formulations. However, a recent report by Levy and Pusey comparing Vigan (BPL 0.5 g sucrose/g immunoglobulin) and Sandoglobulin (Novartis: 1.76 g sucrose/g immunoglobulin) in various indications has shown no such correlation between concentration of sucrose stabiliser in IVIg and propensity to renal failure. In their study of 119 patients given 287 courses of IVIg, eight patients (6.7%) showed a deterioration in renal function regardless of preparation used. On this basis, they concluded that all patients given IVIg should have renal function monitored before, during, and 4–5 days after treatment. This should be compared with the study of Koffman et al., where none of the 46 patients given the same preparation of high dose IVIg had renal dysfunction.

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

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

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

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Table 1 Neurological and neuropsychological findings

<table>
<thead>
<tr>
<th>Preglialome 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>25.7 (2.2)</td>
<td></td>
</tr>
<tr>
<td>UPDRS m&amp;score</td>
<td>15.4 (7.8)</td>
<td>10.8 (5.3)</td>
<td>15.8 (5.9)</td>
<td>5.3 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Levodopa dosage</td>
<td>785 (379)</td>
<td>775 (429)</td>
<td>390 (346)</td>
<td>860 (250)</td>
<td></td>
</tr>
<tr>
<td>Raven’s progressive matrices</td>
<td>39.9 (33.8)</td>
<td>53.9 (36.1)</td>
<td>39.8 (56.3)</td>
<td>62.3 (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 (2.9)</td>
<td>4.9 (2.6)</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 (15.7)</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 (3.9)</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 backwards</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(1,28)=8.84; p<0.01.

Neuropsychological effects of pallidotomy in patients with Parkinson’s disease

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

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

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

Sixteen patients with Parkinson’s disease who underwent unilateral pallidotomy received a 3–6 month follow up. A repeated measures multivariate analysis of variance (MANOVA) for the neuropsychological variables comparing baseline versus 3–6 month
follow up evaluation showed no significant overall time effect (F(7,56)=1.10; NS). There was a significant time effect for the Perdue pegboard test (F(1,44)=30.9; p<0.0001), with a significant improvement in manipulative dexterity over time. A repeated measures MANOVA for the psychophysical variables comparing patients with either a left (n=7) or right (n=9) pallidotomy showed no significant group effect (F(1,16)=0.05; NS), time effect (F(1,7)=1.03; NS), or group-time interaction (F(8,56)=0.22; NS). A repeated measures MANOVA for the psychophysical 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)=0.43; 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 neurological sequelae 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 have also found the neurophysiological sequelae of pallidotomy in a consecutive series of 16 patients with Parkinson’s disease, 10 of whom had a 1 year follow up evaluation. When compared with a group of 20 patients with Parkinson’s disease matched for MMSE scores and age who did not receive a pallidotomy, no significant between group differences were found in the rate of cognitive changes. On the other hand, the pallidotomy group showed a significant improvement on a task measuring manual dexterity compared with the control Parkinson’s disease group. The question now arises as to why pallidotomy in Parkinson’s disease does not produce significant cognitive deficits, given that some case reports described various intellectual problems after spontaneous palilidal 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 of palilidal ablation usually produce a small and localised lesion, whereas spontaneous palilidal lesions 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 Raúl Carrea Institute of Neurological Research-FLENI, and the Fundación Pérez Companc. We thank Fred Byloma PhD for his useful suggestions.

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Response to botulinum toxin in a case of rigid spine syndrome
First described by Dubowitz in 1965, 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.

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

It is important to distinguish rigid spine syndrome from other diseases in which rigidity of the spine can appear, such as Duchenne and Becker’s muscular dystrophies, which characteristically from Emery-Dreifuss muscular dystrophy and from early onset ankylosing spondylitis, as prognoses are different. The rigid spine sign has also been reported in Betz’s myopathy 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.

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 hypoplasia of the jaw, and normal psychomotor development, was being studied by an endocrinologist because of short stature (mother’s stature 145 cm, father’s stature 169 cm) who noticed progressive 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 father had noticed a gradual worsening 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; autoantibodies routinely tested were negative. Complete spine MRI studies ruled out vertebral malformations. An ECG and radiography of the chest were normal. Radiological study of sacral joints was normal and the patient was not diagnosed with HLA-B27 positive. An EMG study showed a myopathic pattern (paraspinal muscle, paracervical muscle, and right quadriceps) with spontaneous activity.

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Injected muscle</th>
<th>1996</th>
<th>1997</th>
<th>1998</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>July</td>
<td>October</td>
<td>January</td>
</tr>
<tr>
<td>Trapezius</td>
<td>30 IU BOTOX* (each trapezius)</td>
<td>50 IU BOTOX*</td>
<td>30 IU BOTOX*</td>
<td>30 IU BOTOX*</td>
</tr>
<tr>
<td>Eternocleidomastoid (ECM)</td>
<td>30 IU BOTOX* (right trapezius)</td>
<td>30 IU BOTOX* (each trapezius)</td>
<td>30 IU BOTOX* (each trapezius)</td>
<td>20 IU BOTOX* (each trapezius)</td>
</tr>
<tr>
<td>Paracervical musculature</td>
<td>30 IU BOTOX* (each ECM)</td>
<td>30 IU BOTOX* (each ECM)</td>
<td>30 IU BOTOX* (each ECM)</td>
<td>20 IU BOTOX* (each side)</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 eternocleidomastoid and 30 IU in right trapezius; on 22 January 1997 30 IU BOTOX were given in each eternocleidomastoid and trapezius; on 21 May 1997 20 IU BOTOX were given in each trapezius; on 25 September 1997 40 IU BOTOX were given in each trapezius and bilateral paracervical 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 esternocleidomastoid and the paracervical muscles, principally the trapezius and secondly the neck flexor and extensor muscular groups, aimed at diminishing the imbalance between the muscle groups. The distribution and percentage of fibre types was preserved and no abnormalities in nerve conduction were found. 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 disorganization have been involved as possible origins of stiffness; weakness of neck flexors 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 Graells for linguistic assistance.

**“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 the pons (fig 1 A). She had not responded to a 4 week course of oral adrenocorticotropic hormone treatment at that time. On admission to our unit there had been no change in her symptoms. On examination she had mild cognitive impairment (mini mental state score 24/30) and a labile affect. She had a bilateral horizontal supranuclear gaze palsy. In addition she had a right upper motor neuron facial palsy and bilateral sensorineural deafness (confirmed by audiometry). Examination of her limbs showed axial and bilateral limb rigidity. She exhibited bradykinesia but did not have a resting 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 studies, and manganese were all negative or normal. Brain MRI showed severe atrophy of the medulla, pons, cerebellum, and middle cerebellar peduncles with cross shaped T2 signal hyperintensity within the pons (hot cross bun sign) and high signal change in the middle cerebellar peduncles (fig 1 B).

**References**


Figure 1 Three different photographs in which progressive amelioration in neck flexion is seen. To make this change objective, we measured the angle between a line joining nasion and tragus and another prolonging the sternum surface. (A) Photograph taken on 22 January 1997. (B) Photograph taken on 24 September 1997. (C) Photograph taken on 15 January 1998.
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 an interested 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, inter-personal 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 Pothala, 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 boundary and 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, veryoften in the context of socioeconomic hardship. Inclusion of qualitative research would have further enriched this book, by bringing their voices more directly into the important debates so elegantly presented. It deserves to become a standard work, available widely to all clinicians and researchers interested in this field.

MOIRA DOOLAN


This short book describes the fascinating recovery and remarkable neurocognitive compensation of Nico, a little boy who at the
Neurobehavioural disability and social handicap following traumatic brain injury—overall the book revisits important generalisations and speculations "information prosthesis". Although some may take issue with some of the generalisations and speculations outlined—the book provides important and compelling evidence of the potential of neuroprosthesis. The previous chapter by Giles "the e-motionary" captured the essence of the book's thesis. Of the treatment chapters, the first part covered "the nature and impact of neurobehavioural disability"; the second addresses "the importance of social and emotional development" and the third is concerned with "models of service delivery". Although the contributors come from the United Kingdom, North America, Australia, the focus (to a large extent) is on British rehabilitation. 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 more 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 heed to this message. BARBARA A WILSON


This book is the result of the author’s long standing interest in and contributions to benign epilepsy, particularly those of occipital origin. It is a truly wonderful 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 fact 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 at any time, in any circumstance, a permanent 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 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 was written over a couple of years ago, but it is comprehensive, a stepping stone to measuring 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 cytogenetic abnormality.”