LETTERS TO
THE EDITOR

Postictal psychosis related regional cerebral hyperperfusion

Postictal psychosis is a known complication of complex partial seizure in particular temporal lobe epilepsy. It usually runs a benign and self-limiting course. A postictal phenomenon with focal cerebral hypofunction (similar to Todd’s palsy), rather than ongoing seizure activity, has been postulated. Surface EEG is either normal or showing non-specific slow waves. Hence, antipsychotic medications are prescribed instead of antiepileptic drugs. Until recently, the pathogenic mechanisms have remained unknown. In this communication, we report on two patients with postictal psychosis, during which a cerebral SPECT study showed a hyperperfusion signal over the right temporal lobe and contralateral basal ganglion. As hyperperfusion in ictal cerebral SPECT is closely linked to epileptic activities, our findings support a contrary explanation for postictal psychosis.

Prolonged video-EEG telemetry study was performed in patients who underwent presurgical evaluation for epilepsy surgery. Antiepileptic drugs were withdrawn to facilitate seizure recording. A diagnosis of temporal lobe epilepsy was based on analysis of the electroclinical events and, if applicable, postoperative outcome after anterior temporal lobectomy. Psychosis was diagnosed according to the fourth edition of the diagnostics and statistical manual of mental disorders (DSM-IV) criteria of brief psychotic disorders without marked stressor. HMPAO-SPECT was performed during the psychotic period, which ranged from 2–4 days after the last seizure. Interictal cerebral SPECT, brain MRI, and a Wada test were performed as part of presurgical evaluation.

Patient 1 was a 34 year old Chinese woman with complex partial seizures since the age of 18. Her seizure control was suboptimal on a combination of antiepileptic drugs. Brain MRI showed a small hippocampus on the right. Interictal EEG showed bilateral temporal sharp waves and ictal recordings confirmed a right temporal epileptogenic focus. A Wada test confirmed right hippocampal memory dysfunction. Six hours after her last secondary generalised tonic-clonic seizure after video-EEG telemetry, she began to develop emotional lability, talking nonsense, motor restlessness, and auditory hallucination. A cerebral SPECT study was performed at day 4 after her last seizure. Her psychotic features persisted although she was taking antipsychotic medication (pimozide). Cerebral SPECT showed a clear hyperperfusion signal over the right lateral temporal neocortex and contralateral basal ganglion. An interictal cerebral SPECT study was repeated at 4 weeks after postictal psychosis which showed a complete resolution of hyperperfusion signal in the right temporal lobe and basal ganglia. Anterior temporal lobectomy was performed and she became seizure free after surgery.

Patient 2 was a 44 year old man with intractable complex partial seizures since the age of 30. His seizures were intractable to multiple antiepileptic drugs. Brain MRI showed left hippocampal sclerosis. Interictal cerebral SPECT showed a relative hypoperfusion area over the left hemisphere. Interictal surface EEG was non-lateralising but ictal EEG disclosed a right hemispheric onset. On withdrawal of antiepileptic drugs, seven complex partial seizures with secondary generalised tonic clonic seizures were recorded within a period of 72 hours. His usual antiepileptic drugs were then restarted. Thirty hours after his last secondary generalised tonic-clonic seizure; he began to develop emotional lability, talking nonsense, restlessness, auditory hallucination, persecutory delusion, and delusion of superstition. Cerebral SPECT study, performed 2 days later while his psychotic features persisted, showed two relative hyperperfused areas over the right temporal neocortex and contralateral basal ganglion in addition to the original hypoperfused area over the left hemisphere. An antipsychotic agent (thioridazine) was
started after the cerebral SPECT. His psychotic symptoms resolved 2 weeks later with full recovery.

Cerebral SPECT performed during the interictal period (IP) and during postictal psychosis (PP) were analysed visually and areas of hypoperfusion were identified. Quantitative data at regions of interest (ROIs) were measured on coronal and axial slides containing basal ganglia (BG), mesial (MT), and lateral (LT) temporal lobe structures. Asymmetry index (ASI) was calculated as (ROI focus−ROI contralateral)/ROI focus×100%. We set an arbitrary change of ASI >100% to be significant. As there were only two patients, statistical testing was not performed.

Both patients showed postictal psychosis and had a regional increase in rCBF over the right temporal neocortex and the left basal ganglia compared to their interictal study (figure). Quantitative analysis for patient 1 showed changes of ASI during IP and PP over right MT was +75% (-6.4647 to +1.65289); over the right LT was +117.6% (1.07727 to 12.55764); and over the left BG was +206.8% (-2.07373 to 2.21574). Quantitative analysis for patient 2 showed changes of ASI during IP and PP over right MT was +38% (13.14217 to 12.64158); over right LT was +178.6% (10.4696 to 18.70077); and over left BG was +159.5% (-5.85566 to 3.27522).

Postictal psychosis is a distinct clinical entity associated with temporal lobe epilepsy. The diagnosis of postictal psychosis requires a close temporal relation between bouts of complex partial seizures and the onset of psychosis. The psychosis usually develops after a cluster of complex partial seizures which are identified by their electro-encephalographic monitoring studies. The clinical course of postictal psychosis is usually benign and predictable. However, the presence of increased rCBF during postictal psychosis, may suggest an alternative explanation as ictal SPECT has been shown to be highly sensitive and specific in demonstrating seizure foci.

To conclude, our results are contradictory to the hypothesis of ongoing angiogenesis. As there were only two patients, statistical testing was not performed. The underlying mechanism of postictal psychosis requires further study.

Tissue samples were obtained after neurosurgical excisions of ruptured AVMs. All 10 AVMs were found to contain large amounts of FN and TN, as shown by intense immunostaining with the use of the IST-9/IST-4 mAbs and the TN-12 Ab fragment. The staining was localised either in the endothelium or the subendothelial layer. A positive response was found in several artery-like vessels and in a few vessels with thinner walls using the TN-11 Ab fragment. The antigen was recognised by the TN-11 Ab fragment showed occurrence of type III repeat C TN isoform in the inner layers of the vascular components of the nidus, irrespective of their morphology.

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The antigens were recombinant protein containing the epitope produced in E Coli. For the mAb BC-1 we used the recombinant protein containing the type-III repeat 7B-8–9. For the mAb IST-4 we used the recombinant protein containing the type-III repeats 2–8. For the recombinant antibodies TN-11 and TN-12 the recombinant type-III repeat C and the recombinant fragment containing the BG isoform were used respectively.

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Previous findings showed that ED-B+FN presents with conformational modifications in its central part and results from deregulation of FN pre-mRNA. The distribution of this isoform was found to be highly restricted in normal adult tissues. By contrast, ED-B+ FN exhibited widespread distribution in the vasculature of fetal tissues, including brain, and of several types of malignancies. It was therefore regarded as a marker of angiogenesis.

Similarly, the type III repeat C TN isoform, recognised by the Ab fragment TN-11, was found to occur in the vascular walls of anaplastic gliomas. Northern blot analysis showed that the mRNA of this isoform was undetectable in normal tissues and some malignancies, but was present in large amounts in fetal tissues, including brain, and in glioblastomas.

Recent advances in the pathology of cerebral AVMs suggest that these lesions might not be static. Tyrosine kinase, an endothelial cell specific receptor upregulated in glioblastomas, was found to be highly expressed in both AVMs and in the vessels of cerebral tissue bordering the malformations, by contrast with the down regulation occurring in the vasculature of the normal brain. The pattern of distribution of structural proteins was consistent with the hypothesis of diffus e activation of angiogenesis, without specific relation to individual vessel types.

Furthermore, use of the cell proliferation marker MB-1 showed endothelial proliferation in arteries, venules, and capillaries of the cerebral tissue neighbouring AVMs.

The present findings indicate that a type III repeat C TN-(A) and ED-B+ FN-(D) isoforms in anagiomatoses vessels. These isoforms are also present in the wall of vessels of the cerebral tissue adjacent to the angiomatous nidius (TN-(A); FN-(D)). Bar=10 μm.

Immunostaining with the TN-11 Ab fragment or the BC-1 mAb shows the presence of the type III repeat C TN isoform containing the ED-B oncofetal domain: a marker of angiogenesis. Int J Cancer 1994;59:612–18.

Hashimoto’s encephalopathy presenting as “myxoedematous madness”

The neuropsychiatric sequelae of hypothyroidism range from lethargy and mental slowing to the florid psychotic illness referred to as “myxoedematous madness”. The last condition is characterised by frank hypothyroidism accompanied by psychosis, and may respond completely to thyroxine. More recently described is a syndrome of subacute encephalopathy, associated with high titres of thyroid autoantibodies, raised CSF protein, EEG abnormalities, and perfusion deficits in the presence of normal structural neuroimaging. In most cases, the encephalopathy occurs without any gross change in circulating concentrations of thyroid hormones, suggesting that an inflammatory process is responsible for the cerebral dysfunction.

In the absence of pathological data, the evidence for a specific pathogenetic mechanism is largely circumstantial: a small vessel vasculitis and immune complex deposition have both been suggested.

Although none of the published cases of Hashimoto’s encephalopathy has described psychosis as a primary feature, it is possible that “myxoedematous madness”, a condition first described in detail by Asher in 1949 lies in a range of encephalopathic phenomena mediated by autoimmune mechanisms. This suggestion would certainly be consistent with the range of clinical presentations of other autoimmune cerebral vasculitides. As autoimmune thyroiditis is the commonest cause of hypothyroid failure in this country, it is likely that cases have been present in at least some of Asher’s original 14 cases. Although most had florid myxoedematous features at psychiatric presentation, this may simply reflect the difficulty in diagnosing subclinical thyroid disease before rapid laboratory assays became widely available. Many features of the present case, however, favoured an endocrine rather than an inflammatory mechanism, suggesting that the condition of “myxoedematous madness”, though rare, remains a valid diagnostic entity.

A 63 year old market stallholder without medical or psychiatric history was brought to a local psychiatric hospital by police several months before rapid laboratory assays became widely available. Many features of the present case, however, favoured an endocrine rather than an inflammatory mechanism, suggesting that the condition of “myxoedematous madness”, though rare, remains a valid diagnostic entity.

A 63 year old market stallholder without medical or psychiatric history was brought to a local psychiatric hospital by police.


became aggressive and threatened them with a saw. The general practitioner was called and suspected a neoplastic process, until a new psyche and a severe depressive illness. Police assistance was requested because of the patient’s continuing violent behaviour.

On admission he was unkempt but cooperative and apparently healthy. He denied depression, but displayed no insight into the irregularity of his behaviour. No psychotic features were seen, although during the admission he consistently rationalised all reported psychiatric phenomena. He was aggressive towards staff and made repeated attempts to abscond. General physical examination was unremarkable. Neurological examination was normal except for spoken language, which was fluent and grammatical, but contained word finding pauses, circumlocutions, and occasional semantic errors (for example, “I just want to get my feet back on the table”). Formal neuropsychological testing, and a screen of laboratory tests for reversible causes of encephalopathy, were performed on admission, and results are presented below (column A). Attention is drawn to his mild naming deficit, and poor performance on the Rey figure, which was due to planning rather than visuospatial errors, suggesting a predominantly “dysexecutive” pattern. CT and EEG were both normal and the SPECT abnormal, which normalised with treatment. By contrast, in the present case the mild and relatively circumscribed neuropsychological deficits coupled with florid psychotic phenomena, also contrasted with the profound global disturbance of cognition usually associated with Hashimoto’s encephalopathy.1

The clinical picture of Creutzfeldt-Jakob disease, one of the human prion diseases, is characterised by rapidly progressive mental and motor deterioration.1 Involuntary movements occur in above 90% of the patients in the course of the disease, the most common being myoclonus, parkinsonism, hemiballism, and dystonia. We report on a patient with CJD who manifested the alien hand sign. We suggest that CJD should be included in the differential diagnosis of diseases which present with an alien hand.

Creutzfeldt-Jakob disease, one of the human prion diseases, is characterised by rapidly progressive mental and motor deterioration.1 Involuntary movements occur in above 90% of the patients in the course of the disease, the most common being myoclonus.1 Other movement disorders range from tremor to the Rey figure and dystonia, and hemiballism.1 We report on a patient with CJD who presented with an alien hand.

Alien hand sign in Creutzfeldt-Jakob disease

The clinical picture of Creutzfeldt-Jakob disease (CJD) includes various movement disorders such as myoclonus, parkinsonism, hemiballism, and dystonia. We report on a patient with CJD who manifested the alien hand sign. We suggest that CJD should be included in the differential diagnosis of diseases which present with an alien hand.

### Table 1

<table>
<thead>
<tr>
<th>Laboratory (units)</th>
<th>A</th>
<th>B</th>
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<tbody>
<tr>
<td>Full blood count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Urea and electrolytes</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Antithyroid antibody</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>B12 and folate</td>
<td>Normal</td>
<td>Not tested</td>
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<tr>
<td>VDLR</td>
<td>Negative</td>
<td>Not tested</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (mU/L)</td>
<td>5.4</td>
<td>0.89</td>
</tr>
<tr>
<td>Free T4 (pmol/L)</td>
<td>1.4</td>
<td>Not tested</td>
</tr>
<tr>
<td>Anti-thyroid microsomal antibodies</td>
<td>25/30</td>
<td>25</td>
</tr>
<tr>
<td>Psysmometric test (normal/abnormal):</td>
<td>10th percentile</td>
<td>16th percentile</td>
</tr>
<tr>
<td>WAIS-R (verbal)</td>
<td>13th percentile</td>
<td>Not tested</td>
</tr>
<tr>
<td>WAIS-R (performance)</td>
<td>27th percentile</td>
<td>Not tested</td>
</tr>
<tr>
<td>FAS verbal fluency (&gt;30)</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>WAIS-R (verbal)</td>
<td>90</td>
<td>11</td>
</tr>
<tr>
<td>Digit span forwards (&gt;5)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Rey-Osterreith complex figure (copy) (36)</td>
<td>Not tested</td>
<td>36</td>
</tr>
<tr>
<td>Rey-Osterreith complex figure (recall) (30%)</td>
<td>Not tested</td>
<td>75%</td>
</tr>
</tbody>
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falling over himself." His wife mentioned bizarre, useless movements of his left hand which were present from the beginning of the disease.

On admission, he was awake, bradyphrenic, and partially collaborative. His conversation was disrupted by halitosis. The affect was sad and he had partial insight for his mental dysfunction. He was disoriented for time, place, and situation. He could understand speech and was able to follow actions involving two consecutive components. Naming was preserved. Prognostic dysphoria and dyscalculia were noticed. Immediate recall and short term memory were severely disturbed, whereas long term memory, especially for personal life events, was relatively spared. Abstract thinking was severely affected. Bimanual movements, such as clapping, were extremely difficult.

The cranial nerves were normal as were ocular fundi. The motor examination showed normal force. Deep reflexes were symmetric and plantar responses were flexor. The right arm had a dystonic posture. His gait was ataxic on a wide base. At times, the left arm would spontaneously rise in front of the patient during speaking or while using his right hand. He was unaware of these movements until they were brought to his attention. When questioned about their purpose, the patient denied that they were voluntary. No grasping of either hand or foot was noticed. Immediate recall and short term memory were severely disturbed, whereas long term memory, especially for personal life events, was relatively spared. Abstract thinking was severely affected. Bimanual movements, such as clapping, were extremely difficult.

The laboratory data including blood chemistries, hematologic, and sedimentation rate were normal, as were folic acid, vitamin B12, and vitamin B12. No myoclonus or pyramidal signs were noticed. Immediate recall and short term memory were severely disturbed, whereas long term memory, especially for personal life events, was relatively spared. Abstract thinking was severely affected. Bimanual movements, such as clapping, were extremely difficult.

The literature seems to describe distinct forms of alien hand. All share the occurrence of involuntary movements contrary to the patient's stated intent, but the types of movement differ. In the callosal form, there are purposeful movements of the non-dominant hand. In the frontal form, there is grasping and utilisation behaviour of the dominant hand. In the corticobasal degeneration, there are aimless movements of either hand. When a consequence of hypovascular or upper limb pathology, alien hands can perform complex acts such as trying to tear clothes or undoing buttons. The description by MacGowan et al has characteristics of the callosal form (especially in patient 2). However, our case suggests that the alien hand sign in CJD may appear in a different type, performing less complex movements which resemble those reported by Riley et al in corticobasal degeneration. These authors described the alien limb as "involuntarily rising and touching the mouth and eyes" (patient 1). The patient thought that she "was powerless to stop this movement" and when directed to stop responded with "the other one." Another patient's left arm was at times "elevated in front of him," while he was "unaware of this situation until his attention was called to it" (patient 10). Another related phenomenon coined as "arm levitation" was reported in progressive supranuclear palsy. In these patients the arm involuntarily raised and performed semi-purposeful movements.

One common denominator between CJD, corticobasal degeneration, and progressive multifocal leuкоencephalopathy, in which an alien hand sign has also been described, is multifocality. In corticobasal degeneration, it was proposed that more than one site is affected or that a "release" phenomenon occurs accounting for the aetiology of alien hand. In CJD, bilateral cortical damage to motor areas might be the origin of their subsequent isolation and disconnection.

We suggest that CJD should be added to the differential diagnosis of diseases presenting with an alien hand with or without myoclonus.

We are indebted to Professor Eran Zardel, Department of Physiology, University of California, Los Angeles, USA.

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Recurrent peripheral neuropathy in a girl with celiac disease

The involvement of the peripheral nervous system (PNS) in children with celiac disease is particularly rare. Furthermore, in both children and adults with celiac disease, neurological complications are chronic and progressive.

We report on a 12-year-old girl affected by celiac disease, who on two separate occasions presented with an acute peripheral neurological syndrome after accidental reintroduction of gluten in her diet.

This patient was born uneventfully to healthy non-consanguineous parents with no family history of neurological or metabolic diseases. At the age of 6 months she was diagnosed as having celiac disease according to the European Society of Paediatric Gastroenterology and Nutrition criteria. Since then she was on a strict gluten free diet and was asymptomatic until the age of 10 years when severe diarrhoea, vomiting, and abdominal pain manifested 6 days after the intake of corn flakes, thought to be gluten free. No previous infections had been noticed. One week after the onset of these symptoms she experienced acute weakness and pins and needles sensation confined to her legs. At that time her parents stopped her intake of corn flakes on the suspicion that these were responsible for the symptoms. Despite this, symptoms worsened during the next 2 days, confining her to bed.

At hospital admission, she was alert and mentally stable. Results of general physical examination were unremarkable. Neurological examination disclosed symmetric, predominantly distal, weakness of the legs; the knee jerks and ankle reflexes were depressed; plantar reflexes were flexor. Distal stocking glove decreased in pin prick and temperature with sparing of proprioception and light touch. Coordination tests were normal.

Laboratory investigations showed a white cell count of 9300/mm³. The results of the following investigations were within the normal limits: haemoglobin, erythrocyte sedimentation rate, serum urea, nitrogen, electrolytes, creatinine, glucose, transaminase, bilirubin, immunoglobulins (Igs), lead, iron, copper, urinalysis, urinary porphyrin, folic acid, and vitamins A, B, B12, and E. Antibodies to Campylobacter jejuni, rotavirus, enterovirus, enteropathogenic Escherichia coli, and antinuclear antibodies were absent. The results of screening for inflammatory and autoantibodies, IgA and IgG antigliadin antibodies (AGAs), IgA and IgG antigliadin antibodies (AGAs), IgA and IgG antireticulin antibodies (ARA), investigated by enzyme-linked immunosorbent assay (ELISA) and immunofluorescence (IF) were also negative. Lumbar puncture was not performed. Antiendomysial antibodies and anti-tTG antibodies were absent. Myelin-associated glycoprotein and myelin...
Electrophysiological study suggestive in both episodes of an acute demyelinating peripheral neuropathy confined to the lower limbs. Values were within normal limits as in the upper limbs

<table>
<thead>
<tr>
<th>1st Episode</th>
<th>2nd Episode</th>
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<tr>
<td><strong>MCV (ms)</strong></td>
<td><strong>Tibial</strong>&lt;sub&gt;1 ν&lt;/sub&gt;</td>
</tr>
<tr>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>74</td>
<td>74</td>
</tr>
<tr>
<td>7.3</td>
<td>8.0</td>
</tr>
<tr>
<td>7.5</td>
<td>8.4</td>
</tr>
<tr>
<td>F wave latency (ms)</td>
<td>70</td>
</tr>
<tr>
<td>CMAP (μV)</td>
<td>Sural&lt;sub&gt;1 ν&lt;/sub&gt;</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
</tr>
<tr>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>16.2</td>
<td>16.2</td>
</tr>
<tr>
<td>16.8</td>
<td>16.8</td>
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</table>

Basic protein were not tested. Nerve conductions were consistent with a predominately motor demyelinating peripheral neuropathy (table). Her symptoms improved spontaneously and was discharged home after 2 weeks. For 2 years she was asymptomatic on a gluten free diet. At the age of 12 she presented acutely with severe abdominal pain 8 days after a weekly intake of bread meant to be gluten free. Two weeks later, due to persisting gastrointestinal symptoms, her parents excluded the bread from her diet. After 2 further weeks, while the abdominal pain was gradually improving, she had a new episode of acute weakness in the lower limbs and sensory abnormalities including burning paraesthesiae. On neurological examination the legs showed marked diminution in muscle power; absent deep tendon reflexes, and a reduction in pain and temperature; light touch, perception of position, and vibration were preserved. Walking was impaired and the patient was bedridden. Otherwise the examination was normal.

A haemogram showed white cell counts of 9700/mm<sup>3</sup>. Laboratory investigations were within normal values as in the past. IgA and IgG AGA, IgA EMA, and IgA ARA assay had been negative. ELISA and IF were again negative. Nerve conduction studies confirmed the presence of a predominantly motor demyelinating neuropathy (table). The parents refused consent for a lumbar puncture or nerve biopsy.

Over the next 2 weeks her neurological disabilities spontaneously improved until full recovery was complete. After 4 weeks, AGA, EMA, and ARA were still negative.

On her most recent admission, 1 year after the onset of her first neurological symptoms, she is still on a gluten free diet and has no residual symptoms or signs.

The natural history of celiac disease is well known and the typical celiac enteropathy is often associated with several other disorders. However, as celiac disease is a relatively common and lifelong condition, it is likely that some of these associations may occur by chance.

This patient, who was diagnosed as having frank celiac disease at the age of 6 months, experienced two episodes of acute peripheral neuropathy, at the age of 10 and 12 years, respectively. Two major pieces of evidence strongly support the assumption of a gluten derived disease: (1) the episodes occurred on both occasions when gluten was accidentally reintroduced in the diet; and (2) the response to a gluten free diet was reasonably rapid, occurring within weeks.

The present case, however, differs clinically from those with neurological involvement previously reported. In the paediatric age group, in fact, neurological complications of celiac disease are rarely encountered and are mostly confined to the CNS: to the best of our knowledge, there are only two previously reported cases of PNS involvement in children with celiac disease. In both cases, however, these were chronic axonal polyneuropathies presenting during a gluten free diet. In both episodes in the present case neurophysiology was strongly supportive of a demyelinating peripheral neuropathy, which is most commonly attributed to a direct immune mediated attack to the myelin. By contrast, what is axonal degeneration may be caused by vascular, and nutritional, metabolic, and toxic factors.

An autoimmune pathogenesis in association with strong evidence of a genetic susceptibility has been proposed for celiac disease. Although it is well established that AGA, EMA, and ARA are reliable indicators of sensitisation to gluten at least at the time of diagnosis, in the clinical practice at follow up, during a gluten challenge, pathological values of these antibodies may not be detected. In the present case the time course of the disease might be suggestive of an antibody mediated response. However, we could not detect pathological concentrations of AGA, EMA, or ARA antibodies either during the course of the disease or at follow up.

It is known that in celiac disease many immunological perturbations can occur outside the gastrointestinal tract. Crossing of the antigens through a damaged small intestinal mucosa, deposition of immune complexes in target organs, a reduction in immune surveillance, mechanism of molecular mimicry, and activated T cell response may contribute to the pathogenesis of the diseases associated with celiac disease. Direct toxic effects of gliadin and vitamin deficiency are other possible pathogenic mechanisms of damage to the nervous system. Although we ruled out a vitamin deficiency it is still questionable whether a toxic neuropathy can be the case.

In conclusion, this case shows two major issues: an acute polyneuropathy can be a complication of celiac disease in childhood and its benign course could help in the understanding of the underlying pathogenic mechanisms.

We are grateful to Professor Angela Vincent (Oxford) for her helpful suggestions in reviewing the manuscript.
examined using a rating scale for the examination of frontal release signs (FRSS), with nine operationally defined items, each on a seven point semiquantitative scale. The nine reflexes were paratonia and palomental, hand grasp, foot grasp, glabellar, rooting, snout, and visual/tactile sucking reflexes. Neuropsychological measures included the assessment of frontal lobe function (trailmaking tests A and B, behavioural dyscontrol scale, and the controlled word association test) and generalised cognitive impairment (CAMCOG). Depression was assessed using the Hamilton rating scale for depression, 15 item geriatric depression scale, and diagnostic criteria for DSM IV major depressive disorder. Family history of depression, suicide to die, and suicidal ideation within the past year were also recorded, as were blood pressure and a checklist for chronic physical illness.

Total FRSS scores and scores on FRSS subscales were compared between groups using the Mann-Whitney U test for independent samples. In the peripheral vascular disease group, a correlation matrix for total FRSS score against DSMIV depression, CAMCOG score, behavioural dyscontrol scale score, verbal fluency score (total number of words beginning with F, A, and S) and trailmaking test times was examined using the Spearman correlation coefficient, corrected for ties. Convergent, sex, blood pressure, and chronic physical illness. Behavioural dyscontrol scale scores, trailmaking A/B test times, and verbal fluency scores were first converted into binary variables according to whether they were at/above or below the median value for the group. CAMCOG score was divided into subjects scoring 69 or above or less than 69. Those associations with a two tailed significance of 0.1 or less were then entered into a linear regression equation using the stepwise method.

Patients with peripheral vascular disease had a higher mean score on the frontal release signs scale than controls (5.9 (SD 4.6) vs 1.7 (SD 1.0)). (Mann-Whitney U = 141, Z = −3.33, two tailed p<0.001), as well as on glabellar and rooting reflexes (table). Only one variable (trailmaking B test time) was entered into the equation; this accounted for 23% of the variance in FRSS score (B=4.6, 95% confidence interval (95% CI) (B) 1.3–8.0, p<0.01).

In peripheral vascular disease, there is limited information available concerning the interaction of neurological and neuropsychological sequelae of coexisting cerebrovascular disease. Phillips et al found greater impairment in psychomotor speed and abstract reasoning in patients with peripheral vascular disease than age/match controls, with less significant differences between the groups in verbal fluency, concentration, abstract thought, perception, and constructional skills.1 Another study by the same group found poorer performance in patients with peripheral vascular disease than controls on visual memory, trailmaking B test, and visuospatial skills. Patients with peripheral vascular disease were also equally impaired in these areas compared with a matched group of stroke patients.2

Small numbers of patients, which may also have obscured other significant findings between the two groups, limit the present study. However, there is some evidence that clinically relevant cerebrovascular disease may accompany peripheral vascular disease and that a prominent disruption of frontal/subcortical brain function may not present with hard neurological signs. As it is possible that silent brain infarction was present in patients with peripheral vascular disease, further studies incorporating brain imaging are required before there can be a clearer understanding of the relation between peripheral and central vascular pathology.

I thank Dr Robert Howard for supervision of this study and Professor Mr Paul Baskerville for allowing me to interview patients under their care. The study was carried out as part of a University of London MD thesis.

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table

<table>
<thead>
<tr>
<th>Hand grasp</th>
<th>Foot grasp</th>
<th>Glabellar</th>
<th>Palomental</th>
<th>Paratonia</th>
<th>Rooting</th>
<th>Snout</th>
<th>Sucking (tactile)</th>
<th>Sucking (visual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>Z</td>
<td>P</td>
<td></td>
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*Higher mean score in people with peripheral vascular disease.

5 years earlier. The angioplasty was complicated by the occurrence of an aneurysm which was thought to be related to dye injection, and phenytoin had been prescribed for a short time thereafter. There was a remote history of heavy alcohol use, but he had been abstinent for several years. His father had had a stroke at the age of 65.

Six months earlier the patient had also collapsed at home and been taken to hospital with a left hemiplegia. Brain CT at that time was normal, as were carotid Doppler studies and an echocardiogram. During that admission to hospital, several generalised seizure-like episodes were seen, some with retained consciousness, and he had again been started on phenytoin therapy. A follow up brain MRI scan was normal and it was concluded that the hemiplegia was non-organic in origin. He was described to have made a gradual, near complete, recovery from this first hemiplegic episode and was scheduled for an imminent return to work at the time of his relapse.

On transfer to this hospital the patient was alert, oriented, and cooperative. Although up to date on current affairs and able to describe the investigations performed at the transferring hospital, he scored only 23/30 on a mini mental state examination, with absent three word recall, impaired registration, and poor copying of a two dimensional line drawing. Further bedside neuropsychological testing showed other findings indicative of constructional apraxia and left hemineglect. Specifically, when asked to draw a clock with the time at 10 minutes to 2 o’clock, all the numbers, and the clockhands, were placed on the right hand side of the clock outline (figure A). Copying of three dimensional line drawings was also significantly impaired (figure B). When asked to bisect a line, the patient did so only minimally to the right of the midpoint (58% of the distance from the left side).

Cranial nerve examination suggested an incongruent and inconsistent left hemianopsia to confrontation testing but was otherwise normal, including bilaterally symmetric optokinetic nystagmus. Motor examination showed paralysis of the left arm and leg, with bilaterally symmetric bulk, tone, and deep tendon reflexes. The plantar response was flexor bilaterally. Sensory examination showed decreased pinprick and absent light touch, joint position sense, and vibration sense on the entire left side. There was also impaired perception of a tuning fork’s vibration on the left side of the forehead, with a distinct demarcation in the midline. The rest of the physical examination was unremarkable.

Brain CT and MRI, CSF examination, and routine EEG were normal. Routine haematological and metabolic analyses plus erythrocyte sedimentation rate, serum lactate, prothrombin time/partial thromboplastin time, fasting serum glucose, HBa1c, serum Ig survey, and thyroid stimulating hormone were all within normal limits. A hypercoagulability profile was negative. A lipid profile showed mild hyperlipidaemia with increased low
density lipoprotein (3.92 mmol/l) and triglycerides (4.30 mmol/l) and low high density lipoprotein (0.73 mmol/l). Serum phenytoin concentration was therapeutic at 74 µmol/l. An ECG was normal.

Ophthalmological consultation and formal visual field testing demonstrated a concentrically constricted field of mild degree in the right eye and tunnel vision in the left eye.

The patient consented to overnight video-EEG monitoring and was seen on multiple occasions to move his left arm and/or leg in a normal fashion, at one point using the left arm to readjust his bed covers shortly after arousal from sleep, before glancing briefly at the video camera and completing the task with his right arm. The prolonged EEG was normal.

A formal neuropsychological assessment performed in hospital documented impaired attention, concentration, and working memory, as well as several atypical calculation errors, the second involving unusual “near miss” letter substitutions or reversals (for example, “amixey”, “executive”). The formal testing identified no consistent evidence of visuospatial deficits or constructional apraxia. The findings were interpreted as inconsistent with the patient’s history but the possibility of a factitious aetiology was not specifically addressed—that is, the patient’s willingness to undergo medical investigations, including video monitoring.

It is unclear how or when the patient acquired the information needed to mimic a constructional apraxia. Previous bedside neuropsychological evaluations may have served to familiarise him with the format of such testing, acting as an impetus to research the issue of stroke and focal brain deficits (which might also have occurred after his father’s stroke), much in the same way he is now researching conversion disorder, thereby discovering what expected answers should look like. Despite repeated questioning, however, no evidence could be gathered from the patient to support this speculation.

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Anosognosia and mania associated with right thalamic haemorrhage

Both anosognosia and secondary mania are associated with right hemispheric lesions. These two non-dominant syndromes, however, are rarely described as occurring together. We present a patient with a right thalamic haemorrhage giving rise to profound denial of hemiplegia and elated mood. This case suggests mechanisms for the common production of mania and anosognosia.

A 53 year old, right handed, black man, with a history of alcohol misuse and dependence and untreated hypertension, was brought to the emergency room a few hours after developing an intense headache and left sided numbness and weakness.

On admission he was described as “belligerent,” “agitated,” and “confused.” Blood pressure was 240/160. Neurological examination disclosed left lower facial droop, decreased left corneal and gag reflexes, and left hemiparesis with dense sensory deficits. With increasing obtundation, the patient was transferred to the intensive care unit and intubated. Brain MRI showed a large, left sided, hyperacute thalamic bleed with mass effect and oedema. The patient was extubated 2 days later and 4 days after the stroke he was described as being drowsy and inattentive, but was able to answer questions...
appropriately. Neurological examination showed contralateral gaze paresis, supra-
nuclear vertical gaze palsy, difficulty converg-
ning, left sided facicul hemiparesis, and dense, 
left sided hemianesthesia. Deep tendon reflexes 
were absent on the left and Babinski's reflex was present on the left. In addition, visual 
extinction and neglect were present. 

At the time of onset of right sided weakness 
the patient insisted that he was “fine,” and 
an ambulance was called over his objections. 
After being examined, the patient acknowl-
edged that he had had a stroke, but, despite 
his hemiparesis, insisted that he was ready to 
go home and go back to work. His belief in his 
ability to walk led to near falls, and he was moved closer to the nurses’ station for closer 
observation. He told the nurses that someone 
else’s arm was in his bed. On one occasion, 
holding up his left arm with his right, he told the nurse to, “take it away; it keeps 
scratching me.” That the left arm “smelled funny” was another reason he wanted the 
nurses to take it away. 

Four weeks after the stroke he first 
acknowledged that his left arm belonged to 
himself, and spontaneously recalled being 
otherwise. By this time he had a moderate 
hemiplegia and recognised “a little weak-
ness,” but continued to insist that he was well 
and able to return to work. By the 6th week 
and the patient more consistently 
acknowledged that he was weak on the left 
side of his body. A request for disabled hous-
ing “so that I won’t be a burden to my family” 
seemed to indicate an appreciation of his 
impairment. He was tinted with guilt, 
within an hour of making such statements the 
patient might insist that after a week’s 
exercise he would be ready to return to work. 
His awareness of his hemiplegia fluctuated 
for 8 weeks. His stroke had not been 
fixed, but remained shallow after 12 weeks; he 
no longer planned to return to work and 
applied for social security disability insurance 
“because they say I’m disabled.” 

The patient’s mood was remarkably cheer-
ful and optimistic. A week after the stroke he 
was noted to praise extravagantly the hospital 
area. He thought of as occurring together, when 
Babinski introduced the term anosognosia he 
used it as part of his own example, in a case in which 
the patient, though not confused, was “a little 
overexcited,” and in a later paper he pre-
sented a case in which there was “a certain 
agitation, which expresses itself by exagger-
ated loquacity, a decrease in attention, and a 
tendency to erotic ideas.” 

Weinstein and Kahn’ noted that euphoria was 
common in patients with anosognosia. Moreover, 
although Cutting' emphasized that apathy 
is the mood more usually associated with 
anosognosia, 10% of his patients with ano-
sognosia were described as having “euphoric 
mood.” 

Right sided thalamic lesions are known to 
produce both anosognosia and mania, but the 
relation of each to the pathology is unclear. 
Only some of the patients with right hemi-
spheric lesions are manic or agnostic. These 
two syndromes may be related to dysfunction 
of different neural networks and only occur 
together when a disease process affects both 
networks. 

Another possibility is that these syndromes 
are aetiologically related. Could anosognosia 
be a manifestation of mania? Although it is 
easy to conceive how elevated mood might 
facilitate anosognosia of hemiplegia (or other 
types of anosognosia), it is difficult to explain 
the presence of denial of ownership and 
dislike of the left arm (other anosognosic 
phenomena) on the basis of euphoria. Moreover, Starkstein et al,” finding that simi-
lar frequencies and severities of major and 
minor depression were present in patients 
with and without anosognosia, suggest that 
a particular mood state may not necessarily 
inflict anosognosia. 

Several explanations have been proposed to 
explain the phenomenon of anosognosia. All 
the models invoke dysfunction of the cer-
ебелльный или парентеральный, что 
интересно, что в этом случае дополнительное МРИ 
failed to demonstrate decreased CBV in the 
parietal lobe. 

In summary, we present a case of mania 
accompanying anosognosia, with a large 
right thalamic haemorrhage. The coexistence 
of mania and anosognosia may be more com-
mon than previously appreciated. The associ-
ation with anosognosia implies that the 
mechanisms implicated in the pathogenesis 
of secondary mania may be similar to those 
of anosognosia. The absence of evidence 
of abnormal parietal, temporal, or frontal lobe 
function by functional MRI in this case is 
intriguing. 

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Epileptic cardiac asystole 

A patient is reported on with habitual 
episodes of collapse and loss of consciousness 
associated with EEG evidence of focal 
epileptiform discharges. Simultaneous EEG 
recordings disclosed 25 seconds of cardiac 
ventricular asystole occurring 24 seconds 
after the onset of electrical seizure activity. 
After changes to antiepileptic medication and 
the insertion of a permanent cardiac pace-
maker he has had no further episodes. In 
cases of epileptic cardiac dysrhythmia, iso-
lated EEG or ECG recordings may prove 
insufficient and prolonged simultaneous 
EEG/ECG monitoring may be required.

Cardiac arrhythmias subsequent to epilep-
tic seizures have been recognised for more 
than 90 years. They provoke diagnostic 
confusion and may be a mechanism of 
sudden unexplained death in epilepsy. 

Whereas sinus tachycardia was noted to 
accompany more than 90% of epileptic seizures, isolated bradycardia was seen much
less commonly (only 1 of 74 seizures recorded). A review in 1996 of the “ictal bradycardia syndrome” showed only 15 documented cases in the literature of either bradycardia or asystole associated with seizures. Most patients had temporal lobe seizures. The longest duration of asystole previously reported is in a 17 year old man with temporal lobe epilepsy who sustained a 22 second pause in cardiac output. More typically the asystolic periods in documented cases are in the region of 5–10 seconds. Shorter duration asystole may not compromise cerebral function sufficiently to cause loss of consciousness. Implantation of a cardiac pacemaker is advocated but does not ensure that lapses of consciousness are eliminated if these are directly related to the seizure rather than to the secondary asystole. We report on a patient with epileptic cardiac asystole of 25 seconds duration demonstrated by prolonged simultaneous EEG/ECG monitoring which responded well to pacemaker insertion.

A previously well 34 year old right handed builder was referred with a 1 year history of fortnightly episodes of loss of consciousness. There was no associated warning, aura, chest pain, or palpitations and the patient was only aware of the episode once consciousness was lost. 16 Channel ictal EEG (eight channels illustrated with ECG) showing electrographic seizure onset and subsequent bradycardia and asystole.

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**Figure 1**: 16 Channel ictal EEG (eight channels illustrated with ECG) showing electrographic seizure onset and subsequent bradycardia and asystole.
restored and he found himself lying on the floor. On recovery there was no confusion, drowsiness, dysphasia, or diuresis. Often, however, he sustained soft tissue injuries to his face and scalp.

Witnesses reported that the patient would, without any apparent provocation, suddenly collapse to the ground where he would remain unresponsive, inaccessible, and motionless for 90 to 120 seconds. On two occasions he appeared confused and disoriented immediately before a collapse. During the period of unconsciousness he would demonstrate no involuntary movements, orofacial automatisms, or cyanosis but he would become pale and “ashen” while staring straight ahead with a glazed look. Occasionally at the end of the episode he would return to normal and within 2 minutes he would have fully recovered. Unusually during one reported episode of unconsciousness he was seen to briefly extend the fingers of both hands.

He was admitted to his local hospital and CT, MRI, interictal EEG, and 24 hour ECG were normal. No episodes were witnessed while he was an inpatient but they were thought to be hypnagogic in origin and therefore he was started on phenytoin, with no benefit. Carbamazepine was added, again with minimal effect.

The patient was then referred to the Epilepsy Assessment Centre of The National Society for Epilepsy and National Hospital for Neurology and Neurosurgery for further investigation and management.

Cardiovascular and neurological examinations were normal and as were MRI and routine interictal EEG. Sixteen channel ambulatory EEG using an Oxford Instruments digital EEG receiver was performed continuously for 340 hours before an episode was captured. Interictally rare spikes were seen over the right frontocentrotemporal region during sleep. The patient was found lying on the floor, regaining consciousness at about 07:06. The event EEG showed a short run of bilateral semirhythmic 2–3 Hz activity at 07:04:34 (figure A), persisting for 8 seconds before being obscured by muscle and movement artefact. Twenty four seconds later, 10 seconds after the first EEG change, at 07:04:58, the ECG changed from sinus rhythm at 90 bpm to a brief period of sinus bradycardia, followed by a period of asystole with only very occasional ventricular complexes. Ninety seconds after the first EEG change (figure B) a few seconds of bradycardia then tachycardia, sinus rhythm was restored. Throughout the episode the QT interval on the ECG remained within normal limits. The EEG became visible again 16 seconds into the asystolic period, at which time it was dominated by diffuse low amplitude slow activity at <1–2 Hz which persisted for 10 seconds (figure C). This was followed by marked attenuation of the EEG activity over the next 10 seconds before large amplitude generalised rhythmic <1Hz activity became apparent. Diffuse theta activity was seen for a further 15 seconds before the EEG returned to its resting state. A VVI permanent pacemaker was inserted. The phenytoin was withdrawn and replaced by lamotrigine. Carbamazepine was left unchanged. The patient was discharged, his medication left unaltered, and at follow up 9 months later reported no further episodes.

Cardiac dysrhythmias are an uncommon but serious consequence of partial seizures. Our case is unusual because of the duration of the cardiac arrest, a series of 26 patients with 74 temporal lobe seizures in which simultaneous EEG and ECG recordings were recorded, ictal arrhythmias occurred in 52% of seizures, the commonest being irregular abrupt changes in heart rate, (both acceleration and deceleration) occurring towards the end of the period of EEG abnormality. Interictally, patients with epilepsy seem no more likely than age and sex matched healthy subjects to experience arrhythmias although in one study patients with epilepsy had a faster ventricular rate and a longer QT interval compared with controls. 

It has been hypothesised that there is laterisation with respect to central autonomic cardiac control with an increase in heart rate seen after an increase in administration of an barbiturate and inactivation of the left hemisphere and a decrease in heart rate on right hemispheric inactivation. Experimental stimulation of the rostral posterior insular cortex in anaesthetised rats has been shown to induce tachycardia and more cause regional stimulation to cause bradycardia. Additionally, prolonged stimulation resulted in ventricular ectopies, heart block, QT prolongation, and death. In patients with temporal lobe patients stimulation of the left insular cortex (particularly posteriorly) produced bradycardia and a depressor response significantly more often than tachycardia and a pressor effect. It is suggested that an epileptic discharge in the insular cortex may result in cardiac arrhythmias.

Recurrent episodes of loss of consciousness are a common clinical problem. An accurate diagnosis relies principally on the patient’s and witnesses’ accounts of events. Further investigations are frequently required which are often normal unless an episode is captured during monitoring. Recording solely the EEG or the ECG may result in erroneous conclusions being drawn and insufficient or inappropriate therapy being instituted. Distinction between a primary cardiac arrhythmia and a secondary central arrhythmia is possible only with simultaneous EEG/ECG recordings.

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Respiratory insufficiency in a patient with hereditary neuropathy with liability to pressure palsy

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant disorder, the neuropathy of which is a 1.5 mb deletion in chromosome 17p11.2 including the peripheral myelin protein-22 (PMP-22) gene. HNPP typically presents recurrent pressure palsies of peripheral nerves, such as the axillary, median, radial, ulnar, or peroneal nerves, at common entrapment sites. Respiratory muscle weakness has not been previously reported in HNPP. We describe a patient with HNPP and respiratory failure and proximal muscle weakness who presented in respiratory arrest at the age of 44. At the age of 47, he noticed a slowly progressive weakness of the pelvic girdle and lower limbs. At the age of 57, he experienced difficulty in going up stairs. However, he was almost independent in daily life. At the age of 60, he was admitted to Sidcot Red Cross Hospital, an emergency patient with a coma due to CO2 narcosis (PCO2 117.6, PO2 64.0). Responding to mechanical ventilatory support, he completely recovered consciousness within a day. His respiratory condition in the daytime improved to that previously. However, he needed mechanical ventilation during sleep because of nocturnal hyperventilation.

The patient had no history of diabetes mellitus, pulmonary disease or another medical condition. There was no familial history of neurological disorder, including entrapment neuropathies. After a few months, he noted that in his teens he had experienced some episodes of right peroneal and right axillary nerve palsies which resolved themselves over a few months.

In a neurological examination, the patient’s mental state and cranial nerves were normal. Evidence of muscular atrophy in the lower limbs lordosis was found. The muscular atrophy was prominent in the shoulder girdle, intercostal muscles, paravertebral muscles, and pelvic girdle, and moderate atrophy was present in all four limbs (figure). There was moderate weakness of the shoulder and pelvic girdle and mild weakness of the distal limbs. The thorax showed poor respiratory movement, and the patient showed paradoxical movement of the abdomen in the supine position. Tendon reflexes were hyporeactive in all limbs. The patient’s sensations of touch and pain were mildly impaired in the four limbs (figure). His position sense was intact. His vibratory sensation was normal. His vital capacity was 1.9 l (55% of the normal mean) in the sitting position, but 1.3 l (38%) in the supine position. The percentage of forced expiratory volume in 1 second was normal (99%) and the forced expiratory volume in 0.7 second was normal (96%). His chest x-ray was normal and pain were mildly impaired in the four limbs (figure). There was moderate weakness of the shoulder and pelvic girdle and mild weakness of the distal limbs. The thorax showed poor respiratory movement, and the patient showed paradoxical movement of the abdomen in the supine position. Tendon reflexes were hyporeactive in all limbs.
ing of the myelin sheath and some abnormality for his technical help with the sural nerve biopsy showed scattered tomaculous thickening of the myelin sheath and some abnormality for his technical help with the sural nerve biopsy showed scattered tomaculous thickening of the myelin sheath and some abnormally thin axonal myelin sheaths. The density of myelinated fibres was reduced (5726/mm²). A gene analysis disclosed a 53% gene dose of PMP-22 related to normal controls, using Southern blots of DNA digested with EcoRI. Given the possibility of superimposing demyelinating neuropathy, especially chronic inflammatory demyelinating polyneuropathy, oral prednisolone (60 mg/day) was given for 1 month. However, the patient’s clinical condition did not respond to this treatment. Pulmonary dysfunction and proximal muscle weakness were almost steady during the next 3 years.

We examined the patient’s elder sister (64 years old), elder brother (62 years old), and younger sister (58 years old), although they had no neurological complaints. All of them had experienced generalised hyporeflexia or areflexia but no weakness or sensory loss, and nerve conduction studies showed moderate conduction slowing with accentuation at the common entrapment sites, suggesting demyelinating neuropathy.

Our patient recalled experiencing recurrent episodes of transit entrapment mononeuropathy, and the familial occurrence of asymptomatic entrapment neuropathy was detected by nerve conduction studies. The presence of tomacula, and genetic analysis confirmed a diagnosis of HNPP. However, the patient’s dominant clinical features—respiratory failure and proximal muscle weakness—were atypical for HNPP. Although respiratory muscle weakness has been reported in hereditary motor and sensory neuropathy (HMSN), there has been no report of respiratory insufficiency associated with HNPP to our knowledge.

The weakness of the truncal muscles, including the respiratory accessory muscle, is a possible cause of respiratory failure in our patient. On the other hand, he had experienced hyperventilation in the supine posture and paradoxical movement of the abdomen, which suggested diaphragmatic weakness.1 Also, chest radiography showed poor movement of the diaphragm. Although the prolongation of distal latency in the phrenic nerve was mild considering the severity of respiratory failure, assessment of axonal loss is not possible with phrenic nerve stimulation. In fact, phrenic nerve latency is not necessarily associated with pulmonary dysfunction in HMSN.2

Diffuse proximal weakness in our patient is an uncommon finding as for HNPP. Mancardi et al4 reported on three patients with progressive sensory-motor polyneuropathy associated with 17p11.2 deletion, and the initial symptom of one patient was proximal weakness in one arm. We propose that our patient represents a clinical phenotypic variability among HNPP. It may be necessary to pay attention to respiratory function in HNPP.

We thank Dr T Yamamoto from the University of Occupational and Environmental Health for the gene analysis and Mr T Nagase from Chiba University for his technical help with the sural nerve biopsy.

Spinal accessory neuropathy and internal jugular thrombosis after carotid endarterectomy

Spinal accessory neuropathy is a rare complication of carotid endarterectomy (CEA).1 Internal jugular venous thrombosis after CEA has also been reported rarely, but is likely more common; as internal jugular

venous thrombosis is often asymptomatic, or presents with non-specific pain, it is probably unrecognised in many cases.\(^1\) Concurrent ipsilateral spinal accessory neuropathy and internal jugular venous thrombosis after CEA is expected to be rare, and this is underscored by the lack of published cases. Despite this apparent rarity, a common pathogenetic mechanism for postoperative spinal accessory neuropathy and internal jugular venous thrombosis may well be present, at least in some cases, which may lead to the consideration of the possibility of both when either is discovered.

We report on a patient who developed right spinal accessory neuropathy and internal jugular venous thrombosis after right CEA. A 59 year old man underwent right CEA for possibly symptomatic stenosis. Angiography had shown 90% stenosis of the right internal carotid. The operation was done under general anaesthesia. The carotid bifurcation was unusually distal, necessitating a long dissection and high retraction. No immediate postoperative complications were evident. The next day, the patient complained of mild pain at the operative site, but did not notice any weakness. The pain spread into his right shoulder within several days; at that time, he also noted difficulty raising his right arm. His symptoms worsened further a few weeks later. The symptoms persisted and he presented for neurological evaluation 4 months after CEA. At that time, he had some induration along the incision site and a palpable cord within the right supraclavicular fossa. There was moderate atrophy of the right sternocleidomastoid and trapezius, with right shoulder drooping and minor right scapular winging. Right arm abduction produced more prominent scapular winging and was limited to 90 degrees due to pain and weakness. Electrodagnostic studies were consistent with partial right accessory neuropathy with minor denervation of the right trapezius. Cervical ultrasonography and MRI demonstrated right internal jugular venous thrombosis. The patient was treated with a shoulder support, analgesics, and low dose aspirin. There was no significant clinical change 1 year after CEA. Repeat electrodagnostic studies were consistent with chronic right spinal accessory neuropathy, and repeat ultrasonography showed persistent right internal jugular venous thrombosis. Spinal accessory neuropathy was first reported as a complication of CEA in 1982.\(^2\) Since then, there have been several case reports and small series.\(^2\) A 1996 review of reports of cranial neuropathy after CEA disclosed only one patient with spinal accessory neuropathy in over 3000 cases.\(^2\) Although the authors did not include several other reports\(^2\) which, taken together, may seem to suggest a somewhat higher incidence, the overall small number of reported cases in proportion to the hundreds of thousands of CAs that have been done worldwide suggests that clinically significant spinal accessory neuropathy is a rare complication. Minor spinal accessory neuropathy after CEA may be more frequent. The cause of spinal accessory neuropathy after CEA is usually not well established, but intraoperative nerve stretching or compression from retraction is most often invoked.\(^2\) Delayed onset (after 3 weeks) has been noted in some; for these patients, postoperative inflammation and scarring seem more likely causes. Spinal accessory nerve transection or ischemia/infarction (arterial or venous) are other possibilities. As in our patient, high carotid resection and retraction have been reported to precede spinal accessory neuropathy.\(^4\)

The spinal accessory nerve courses along the internal jugular vein and near the internal carotid artery, typically well above the carotid bifurcation. It is thought that a high incision and retraction resulting from a high carotid bifurcation would place the nerve at risk. Whether this realisation may lead to any technical modification to decrease the risk of spinal accessory neuropathy in those with a high bifurcation is unknown.

From our search, internal jugular venous thrombosis after CEA has been reported in only one case.\(^3\) As Southcott et al noted, retraction of the internal jugular during CEA may cause thrombosis from venous stasis or endothelial injury. Other causes of internal jugular venous thrombosis include jugular cannulation, blunt cervical trauma, and a hypercoagulable state. Internal jugular venous thrombosis may occur soon after neck dissection, often with recanalisation after several months.\(^3\)

The presence of induration about the incision site and a palpable supraclavicular cord in our patient led us to suspect venous thrombosis. Other causes of spinal accessory neuropathy may often be asymptomatic. Potential symptoms of internal jugular venous thrombosis include headache, dysphagia, and anterolateral neck pain, tenderness, and swelling. In addition to paresthesia, urination, fever and leucocytosis may occur.\(^3\)

Common pathogenetic mechanisms for spinal accessory neuropathy and internal jugular venous thrombosis may include intraoperative traction, haematoma, and postoperative inflammation and scarring.

Although the onset of either spinal accessory neuropathy or internal jugular venous thrombosis in our patient cannot be determined precisely, it is likely that both developed at about the same time. The delayed worsening of the spinal accessory neuropathy in this case suggests postoperative scarring or inflammation. The lack of improvement after a year, as in some other cases of spinal accessory neuropathy after CEA, implies considerable axonal injury, but does not clarify the manner of injury.

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Ischaemic stroke in a sportsman who consumed MaHuang extract and creatine monohydrate for body building

We report the first case of extensive cerebral infarct in a young sportsman consuming high doses of MaHuang extract and creatine monohydrate. This should raise awareness in the community to possible serious adverse effects of energy supplements.

A 33 year old man had a severe aphasia on awakening in the morning of 23 January 1999. He did not complain of other symptoms. He was referred to our department on 26 January 1999. He had a Wernicke aphasia with a slight right sided face and arm weakness and a right Babinski sign. His blood pressure was 140/60 and his pulse 54 per minute. Brain CT showed signs of extensive left middle cerebral artery infarct. Cervical ultrasound duplex scanning and cervical angiography were normal. Cerebral CSF examination and EEG were also normal except for a patent foramen ovale.

The patient had no vascular risk factors, in particular no tobacco use, and he was perfectly fit until his stroke. He was a sportsman with 2 hours daily intensive training for body building. He was working as a baggage handler in an international airline company. During a recent journey to Miami, Florida, he bought tablets of “energy pills” in a shopping mall to enhance his athletic performances. The first drug contained MaHuang extract (corresponding to 20 mg ephedra alkaloids), 200 mg caffeine, 100 mg L-carnitine, and 200 µg chromium per two capsules. The second drug contained 6000 mg creatine monohydrate, 100 mg taurine, 100 mg inosine, and 5 mg coenzyme Q10 per scoop. He consumed 40–60 mg ephedra alkaloids, 400–600 mg of creatine monohydrate daily for about 6 weeks before his stroke.

Although a paradoxical embolism through a patent foramen ovale in this patient cannot be ruled out as he recently returned from a transatlantic flight, there was no deep venous thrombosis and D-dimers were normal. However, ephedrine has an indirect sympathomimetic action and is used mainly for arteriolar vasodilatation in addition to other catecholaminergic effects. Both ischaemic and haemorrhagic stroke associated with ephedrine use have been reported.\(^3\) Acute myocardial infarction and acute psychosis have also been reported after taking ephedrine and other sympathomimetic drugs.\(^1\) Ephedrine and its metabolites are natural products that are used in non-prescription medicines for multiple uses. Some products under the的品牌 as in our patient. Renal dysfunction has also been reported after oral creatine supplements. Our patient had a slight increase in creatine concentration although...
it remained in the normal range. Whether the use of high doses of caffeine can enhance the cardiovascular effect of ephedrine remains a possibility as stroke after taking a combination of caffeine and amphetamine has been reported.1

Drug addiction in sportsmen and sportswomen is becoming a major concern in our societies, involving both professionals and amateurs. As energy supplements, thought to enhance performance, are easily available in some countries without the need of medical prescription, everybody should be aware that these so-called “benign” drugs may have major adverse effects.

This first case report of an extensive cerebral infarct in a young sportsman consuming high doses of MaHuang extract and creatine monohydrate should alert the sport community to this possible adverse effect of energy supplements, particularly when used in multiple combination.

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Petroclival meningioma as a cause of ipsilateral cervicofacial dyskinesias

Hyperkinetic movement disorders of facial and neck muscles such as blepharospasm, hemifacial spasms, facial myokimia, and cervical dystonia have rarely been associated with unilateral brainstem or posterior fossa pathologies. We report a case of unilateral cervicofacial dyskinesias due to an ipsilateral petroclival meningioma.

A 32 year old left handed woman complained about left sided facial dysesthesia of the upper quadrant of her face for 1 year. In addition she had intermittent ipsilateral headache. A left sided facial palsy and hypogeusia developed. When progressive hearing loss and persistent ipsilateral tinnitus occurred she sought medical advice. She was referred to our department for further treatment after a large tumour in the left cerebellopontine angle had been demonstrated by MRI. On admission, the left corneal reflex was absent. There was marked hypoaesthesia of the first two divisions of the left trigeminal nerve and a mild left facial palsy. There was also hypogeusia of the left half of the tongue. Speech was slightly dysarthric. During examination dystonic and choreic movements of the left facial muscles were seen. The dystonic grimacing increased when the patient was being observed. There were also intermittent jerky dystonic head movements with turning of the head to the left, associated with slight elevation of the left shoulder. The facial movement disorder was clearly different from hemifacial spasm. There were no tonic or clonic synchronous contractions of facial muscles and no signs of involuntary coactivation. The patient barely noted the dyskinesias. Audiometry showed a hearing threshold at 30 Db on the left side and lack of stapedius reflex on the left side. Oculovestibular response to caloric stimulation was...
decreased on the left side. Furthermore, there was mild left dysdiadochokinesia. Neurography of the facial nerve was normal on both sides. Needle myography of the left frontalis and orbiculari oculi did not show signs of denervation.

An MRI study showed a large gadolinium enhancing tumour within the left cerebellar pontine angle extending to the cavae Meckeli with marked displacement of the brainstem to the contralateral side (figure A and B). Postoperative angiography showed a discrete blush of the tumour as typically seen in meningiomas. The tumour was totally removed by a combined transpetrosal supratentorial and infratentorial presigmoidal approach. The postoperative course was uneventful and there were no new deficits. The facial palsy improved slightly as well as the trigeminal hypoaesthesia. Audiometry remained unchanged. Postoperative imaging showed no residual tumour and the displacement of the brain stem within the posterior fossa had resolved (figure C). Marked improvement of the left sided craniofacial dyskinesias occurred during the next weeks.

The postoperative improvement of the dystonic and choreic grimacing and the cervical dystonia indicates a causal association between the petroclival meningioma and the segmental hyperkinetic movement disorders. Such a relation is supported also by the absence of a family history of movement disorders and the absence of previous exposure to neuroleptic medication. Hyperkinetic movement disorders due to tumours of the brainstem or of the posterior fossa have been reported only rarely. Asymmetric blepharospasm was recently found in a patient with an ipsilateral mesencephalic cyst.1 Hemifacial spasm was seen in paresis of cranial nerve V, and epidermoid tumours of the cerebellopontine angle.2 Acoustic neuromas and anaplastic pontocerebellar glioma can be associated with facial myokymia and spastic paretic facial contracture.3 Also, cervical dystonia due to tumours of the cerebellopontine angle have been reported recently.4

The pathophysiological mechanisms responsible for dystonic movement disorders caused by structural or functional lesions of the brainstem are not fully understood. The possibility of denervation supersensitivity of cranial nerve nuclei has been proposed previously. Alternatively, enhanced excitability of brainstem interneurons has been suggested.5 This pathophysiological mechanism is supported by the findings of blink reflex studies in patients with blepharospasm, spasmodic dysphonia, and cervical dystonia. Tolosa et al found significantly less inhibition of the test stimulus polysynaptic late response and marked enhancement of the recovery curve of the late response under such conditions compared with the response in healthy subjects.6 The late response under such conditions comprised a discrete blush of the tumour as typically seen in meningiomas. The tumour was totally removed by a combined transpetrosal supratentorial and infratentorial presigmoidal approach. The postoperative course was uneventful and there were no new deficits. The facial palsy improved slightly as well as the trigeminal hypoaesthesia. Audiometry remained unchanged. Postoperative imaging showed no residual tumour and the displacement of the brain stem within the posterior fossa had resolved (figure C). Marked improvement of the left sided craniofacial dyskinesias occurred during the next weeks.

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Acute multifocal cerebral white matter lesions during transfer factor therapy

Transfer factor is an active substance of unknown structure present in dialysable leukocyte extract which is assumed to transfer cell mediated immunity in an antigen specific fashion.7 The mechanisms of action of transfer factor are still far from clear; in vitro dialysable leukocyte extract increases macrophage activation and interleukin (IL) 1 production and enhances leukocyte chemotaxis and natural killer function. Transfer factor has been reported to stimulate the cell mediated antigen specific response in patients with various infections8; therefore, treatment with transfer factor has been suggested in patients with selective deficits in cell mediated immunity such as some refractory neoplasms and chronic infections. Moreover, it has been used in the treatment of uveitis.9 Administration of dialysable leukocyte extract has been claimed to transfer immunological memory.10 We report on a patient in whom multiple cerebral white matter lesions developed after taking dialysable leukocyte extract orally for 4 years. A 28 year old man was admitted to hospital because of headache, mental confusion, and right hemiparesis. He had recurrent bilateral uveitis from the age of 12 to 14 with recent unilateral uveitis in the left eye. In January 1995 retinal vasculitis was diagnosed at fundoscopy and in July 1995 he started oral transfer factor as dialysable leukocyte extract twice a week. He complained of generalised weakness after the second dose and the referring symptoms developed after the third dose.

Neurological examination on admission showed mental confusion and severe right spastic hemiparesis with a Babinski’s sign. No fever or menin geneosis was present.

Laboratory examinations on admission showed a slight increase in total serum protein (8.4 g/l, normal 6.0–8.0 g/l), although the serum protein fraction was normal, antistreptolysin titres (355 UI/ml, normal <200 UI/ml), and antideripilin IgG (30 UI/ml, normal 12 UI/ml). Negative results were obtained for HIV test and serum immunoglobulins, venereal disease laboratory test, erythrocyte sedimentation rate, fibrinogenemia, C reactive protein, rheumatoid factor, Wäaler-Rose, protein electrophoresis, antinuclear, anti-DNA, antiniminoclonal, anti-ENA, anti-smooth muscle, and antineu̇rophil cytoplasmic antibodies, lupus anticoagulant, cryoglobulins, immune complexes, complement fractions, and neoplastic markers.

Sero logical investigations showed IgG but not IgM against cytomegalovirus (CMV), Herpes simplex, Varicella zoster, Epstein-Barr virus, Coxsackie, Adenovirus, Enterovirus or Borella burgdorferi were present. Polymerase chain reaction search for Herpes simplex 1 and 2, Varicella zoster, CMV, Epstein-Barr virus, and JC virus in the CSF was negative. Cell, protein, and glucose concentrations in CSF were normal. No oligoclonal bands or antibody against CMV, Herpes simplex, Varicella zoster, Epstein-Barr virus, Coxsackie, Adenovirus, Enterovirus or Borella burgdorferi were present. Polymerase chain reaction search for Herpes simplex 1 and 2, Varicella zoster, CMV, Epstein-Barr virus, and JC virus in the CSF was negative.

Brain MRI showed several extensive asymmetric lesions in the subcortical and periventricular cerebral white matter, some of which exerted a mass effect on the nearby CSF spaces. All lesions exhibited thick ring-like enhancement after intravenous contrast administration (figure). The brain stem, cerebellum, and cervical spinal cord were spared.

The patient had a progressive spontaneous remission of symptoms and signs. The neurological examination 20 days after onset showed slightly increased deep tendon reflexes on the right side and was normal 40 days later; all laboratory analyses were normal except for antistreptolysin titer (265 UI/ml). Two MR scans at 1 and 4 months after onset showed progressive reduction of the extension of cerebral white matter lesions, which did not show contrast enhancement. A final MR scan 20 months after onset showed further regression of lesions without contrast enhancement and a new large lesion in the left occipital white matter, which showed moderate contrast enhancement. At present, after 5 years, the patient is in a good state of health and neurological examination and laboratory tests are normal.

The close temporal relation between assumption of dialysable leukocyte extract therapy and appearance of cerebral white matter lesions in our patient supports the possibility that the association of the two events might not be causal. Despite the absence of biopsy, we reasonably excluded...
the diagnosis of vasculitis or neuro-Bechet's disease although in the absence of biopsy. In fact, the clinical, laboratory, and MRI findings were not typical and a low titre of antistreptolysin antibodies is found in 2% of healthy subjects.1

The occurrence at different time of focal cerebral white matter lesions highly supports the diagnosis of multiple sclerosis, but some clinical and laboratory findings in the patient are not typical for this condition. Mental confusion is not common at the onset of multiple sclerosis whereas it is often found in acute disseminated encephalitis.2 In addition, CSF without oligoclonal banding argues against a diagnosis of multiple sclerosis, whereas it is commonly found in acute disseminated encephalitis.3 On the other hand the possibility that acute disseminated encephalitis may recur has been accepted4 and on the basis of the patient's clinical picture and CSF, we favoured such a diagnosis.

The pathogenic mechanisms underlying the triggering, development, and duration of multiple sclerosis and acute disseminated encephalitis are still far from clear despite the progress made in unravelling them. Some findings suggest that acute disseminated encephalitis and multiple sclerosis lie at the two poles of an autoimmune range, in which autoantigen reactivity is only temporary and direct against a single antigen in acute disseminated encephalitis and multiple antigens in multiple sclerosis.

Although the hypothesis that dialysable leucocyte extract had triggered an autoimmune disorder in our patient cannot be proved, our finding is in line with the report of multiple cerebral lesions after therapy with interleukin-2.5 On the other hand, the fact that acute disseminated encephalitis is often correlated with infections such as during vaccinations or viral infections6 led us to postulate in this patient a cell mediated immunological mechanism. Therefore, an immunological cross reaction between viral antigens (or other foreign material contained in vaccines) and various parts of the nervous system resulting in acute disseminated encephalitis might have occurred. As already noted, dialysable leucocyte extract contains a multitude of immunostimulating or potentially activating substances so it is impossible to pinpoint which one could have been responsible for the demyelinating effect seen in our patient. This notwithstanding, our finding indicates that neurological surveillance is worthy in patients assuming dialysable leucocyte extract therapy.

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Fahr's disease and Asperger's syndrome in a patient with primary hypoparathyroidism

Abnormal calcium phosphate metabolism has not previously been associated with Asperger's syndrome, a form of pervasive developmental disorder. Nor have symmetric calcifications of the basal ganglia, dentate nuclei and cortex, or Fahr's disease7—whether idiopathic or associated with hypoparathyroidism—previously been associated with this handicap. We present the case of a 24 year old man with Asperger's syndrome, primary hypoparathyroidism, and multifocal brain calcifications.

According to medical history, the patient's mother had received weekly injections of Depopovera during pregnancy. A single child born after a normal term delivery, he underwent surgery for an inguinal hernia at 3 weeks. Developmental milestones were only moderately delayed. At 9 months, he rolled instead of crawling. He walked at 15 months, spoke at 2 years with poor articulation, and still speaks in short, unelaborated sentences. His social and language development lagged behind grade school and he occasionally got into fights. In late adolescence, antisocial behaviour took the form of shoplifting and repeated long distance calls to pornographic hot lines. As an adult, his social adaptation remains poor: he currently lives with his mother and works irregularly as a dishwasher in a restaurant. He is indifferent, isolated, and resists novelty. He enjoys repetitive and solitary activities such as slot machine games and playing the piano.

Neurological examination showed bilateral hyperreflexia, mild imprecision of fine finger movements, dysgraphaesias on sensory testing, and a manneristic gripping handshaken. There were no extrapyramidal...
symptoms. His IQ score was in the low range (WISC-C=85 at the age of 13; Barbeau-Pinar=82 at the age of 17). He also presented an impairment on the Tower of London test, which measures executive function, and in a task assessing the understanding of others’ intentions. These two findings are reliably present in pervasive developmental disorders, in this IQ range. In addition, his performance on the Tower of Toronto test disclosed impaired performance in procedural learning. Psychiatric assessment showed scores above the cut off for autism according to the autism diagnostic interview (ADI),3 a standardised interview that requires specific training and those administering it to have a 0.90 reliability with other researchers. The subject was positive for the diagnosis of autism, being above cut off values in the three relevant areas of communication, social interactions, restricted interests, and repetitive behaviours. Nevertheless, he did not present delay in language acquisition or morphological atypicalities in language development, which corresponds to DSM-IV criteria for Asperger’s syndrome.

Brain CT showed dense calcium deposits in the basal ganglia, thalamus, cerebellar dentate nucleus, and orbitofrontal cortex, consistent with Fahr’s disease (figure). Serum CT showed increased activity in the basal ganglia relative to the cerebral cortex. A fine banded karyotype was normal. Serum calcium was 1.55 mM (normal 2.15–2.55 mM), phosphate 1.69 mM (normal 0.70–1.5 mM), ionised calcium was 0.80 mM at pH 7.4 (normal 1.19–1.34 mM); urinary calcium was 0.8 mM (normal 2.5–6.3 mM). Serum parathyroid hormone was below 0.6 pmol/l, 25 hydroxyvitamin D was 77 nmol/l (normal 50–200 nmol/l), osteocalcin was 1.6 pmol/l (normal 0.3–2.4 pmol/l), C-telopeptide of type I collagen was 1.4 pmol/l (normal 0.4–2.2 pmol/l) and bone alkaline phosphatase was 426 IU/l (normal 30–110 IU/l). A bone biopsy showed fibrous and almost disintegrated bone trabeculae. The patient regained normal neurological function. Over a 3 year follow up period there was no recurrence.

Fahr’s disease consists of symmetric calcifications, located mainly in the basal forebrain and cerebellum, which are of various astetologies. Cognitive and behavioural abnormalities may be present when calcifications occur early in development. A fortuitous association between pervasive developmental disorder and Fahr disease is suspected from replicated findings of executive function deficits and from occasional findings of front hypometabolism or abnormal macroscopic brain morphology. Abnormal cell counts and morphology in the cerebellar hemispheres have also been reported, but the relation of these findings to autism is controversial.4

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Hypertrophic atlantoaxial ligaments: an unusual cause of compression of the upper spinal cord

The craniovertebral junction can be affected by several pseudotumorous masses extradurally located, such as rheumatoid panus, hypertrophic non-union of odontoid fracture, post-traumatic cicatrix, synovial cysts, tumorous calcium pyrophosphate dihydrate crystal deposition, taphoencephous gout, calcification of the posterior longitudinal ligament, synovial disease-like pigmented villonodular synovitis, and synovial chondromatosis.1–3 Hypertrophy of the atlantoaxial ligaments as a consequence of degenerative disease was recently recognised as an individual entity. Only five previous cases have been published.6 We add another case to the short series available in the literature, emphasising that as the cause of the spinal cord compression is amenable to surgical removal, symptomatic patients should be diagnosed and treated without delay.

A 66 year old woman presented with a rapid development of progressive spastic tetraparesis and an unremarkable medical history. There was no osteolysis or instability on plain cervical radiography and C.T. A bone scan with 99 mTc was unremarkable. Magnetic resonance imaging showed a retro-odontoid extradural mass that was homogeneous and isointense on T1 weighted signal, demarcated no enhancement after intravenous gadolinium contrast, and was compressing the upper cervical spinal cord (figure). The laboratory tests were normal, confirming the absence of rheumatoid arthritis, metabolic disease, or gout. Surgical removal via a transtoral approach with a minimal bony resection was direct and provided sufficient space to obtain spinal cord decompression. It was followed by a posterior C1-C2 fusion. Macroscopically, the lesion had no capsule and resembled a hypertrophic ligamentum flavum. Microscopically, it was non-inflammatory, hypocellular, and ligamentous pieces found within the mass appeared fibrous and almost disintegrated. The patient regained normal neurological function. Over a 3 year follow up period there was no recurrence.

We focus attention on hypertrophic atlantoaxial ligamentary disease as a degenerative disease that must be considered within the possible causes of high spinal cord compression.

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Selective hemihypaesthesia due to tentorial coup injury against dorsolateral midbrain: potential cause of sensory impairment after closed head injury

A 63 year old woman who fell off her bicycle had a left temporal region head injury with evidence of initial loss of consciousness of 5 minutes and scalp excoriation of that area. On arrival at our hospital 30 minutes later she was alert and oriented. Cranial nerve functions, including extraocular motion and hearing function, were preserved. Pain and temperature sensations of the right side, including her face, showed a 70% decrease compared with the left side; however, position and vibration sensations were normal. Other neurological examinations, including motor function, coordination, and deep tendon reflex, were normal. The patient’s only complaints were left temporal headache and right hemihypaesthesia.

Brain CT on admission showed a discrete and linear high density at the left ambient cistern without other intracranial lesions. On the next day CT showed an obscure low density lesion at the dorsolateral midbrain in addition to the previous lesion (figure). Brain MRI, taken 3 days later, demonstrated an intraparenchymal lesion, at the surface of the left dorsolateral midbrain in high intensity on a T2 weighted image. The high intensity lesion corresponding to haematoma on CT was seen in the ambient cistern (figure). Taking both CT scans and MRI into consideration, this case was diagnosed as traumatic midbrain contusion.

The loss of pain and temperature sensation improved gradually and the patient was discharged 2 weeks later. T2 weighted images 1 month later showed a more localised lesion in the same area. The coronal slices showed a high intensity lesion at the level of lower midbrain coinciding with the tentorium, disclosed as a low line between the occipital lobe and the cerebellar hemisphere (figure). The neurological deficits almost disappeared 6 months later.

Somatosensory impairment including pain is one of the most common complaints among patients with cranioceval injury. Responsible lesions for sensory impairment, detectable by neuroimaging studies, almost always accompany associated neurological deficits. To our knowledge, a selective injury at the spinothalamic or trigeminothalamic tracts due to closed head injury has not been highlighted in the neurological literature.

The MR images in our case showed a discrete lesion at the left dorsolateral midbrain. Topographical study at this lower midbrain level showed that the lateral and ventral spinothalamic and ventral trigeminothalamic tracts pass at the surface of this level by carrying a superficial somatosensory input. The lesion shown in our MR images seemed to be localised to these tracts. The medial lemniscus for the deep sensation and lateral lemniscus and nucleus of inferior colliculus associated with hearing function run ventral and dorsal to these tracts, respectively; which were seemingly spared in our patient. The topographical anatomy seemed to correspond to the neurological manifestations of our patient.

The mechanism of midbrain injury in our patient was speculated to be due to tentorial coup injury based on MR images. The location of contusion was at the lower dorsolateral midbrain, coinciding with the tentorial edge on the injured side, tentorial contact to the midbrain supposedly occurred more readily. Brain MRI findings support the anatomical features of this tentorial coup injury. This injury is not rare in patients with severe head injury, accompanied by other intracranial lesions, and is often caused by lateral displacement of the brain stem relative to the tentorium. It is influenced by congenital variation in the size and shape of the tentorial incisura. The brain stem of the patient with a narrow incisura is more vulnerable to the direct contusive effects than that of a patient with a wider incisura. Therefore, even in minor head injury, this mechanism may occur in patients preconditoned with narrow tentorial incisura, which may have been the case in our patient.

The concept of tentorial coup injury against the midbrain is not new. It usually accompanies various degrees of conscious disturbance and other long tract signs, sensory deficits as well as cerebellar and cranial nerve palsy due to the midbrain lesion or other associated intracranial lesions. The clinical manifestation of our patient may represent one of the mildest forms of the midbrain contusion. The question then when we see a patient with post-traumatic sensory deficit, the possibility of this tentorial injury should be kept in mind even in minor head injury.

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Toluene induced postural tremor

We read with interest the article by Miyagi et al1 and comment on the medical treatment of toluene induced tremor. Microdialysis experiments in rats have shown that inhalation of toluene increases extracellular γ-amino butyric acid (GABA) concentrations within the cerebellar cortex which probably explains why GABA agonists including benzodiazepines (for example, clonazepam) are not very effective in toluene induced tremor and ataxia. Rat experiments also showed a 50% reduction in brain catecholaminergic neurons.2 Degeneneration of certain cerebellar pathways is probably responsible for the loss of this dopaminergic innervation.2 Dopamine agonists could therefore be of potential interest in the treatment of toluene induced tremor. This hypothesis was explored in a recently described case,3 which showed remarkable clinical and iconographic response to amantadine hydrochloride.4-Tolocin Clin Toxicol (in press).


Early diagnosis of subependymal giant cell astrocytoma in children with tuberous sclerosis

Nabnout et al4 have attempted to identify the risk factors for the progression of subependymal nodules into giant cell astrocytomas (SEGAs) in the tuberous sclerosis complex. In attempting to develop screening strategies that avoid iatrogenic morbidity, patient inconvenience, and excess cost, it is essential that the natural history of these lesions in the general population of patients with tuberous sclerosis complex be understood well.

We think that there are two problems with this study that should make the physician cautious about accepting the factors identified by Nabnout et al4 as a basis for a screening programme. The first is that this study was performed in a population that had been referred to a tertiary medical centre, and then had been further selected by virtue of having had at least 3 years tertiary centre follow up and needing two MR scans of the head. The prevalence of astrocytomas and risk factors, and hence the positive predictive value of any screening test in a general population of patients with tuberous sclerosis complex is likely to be different from those described in the highly selected group studied in this paper. The second is that the authors have made a potentially misleading decision to exclude more than half their study sample because they do not have lesions close to the foramen of Monroe. It is not certain that all SEGAs arise from lesions close to the foramen. They may arise in the fourth ventricle. Furthermore, the late presentation of many lesions in the lateral ventricles has, in the past, precluded accurate determination of their point of origin. Thus the study selects 24 of 60 patients who had met their entry criteria but does not state how many of the excluded 36 patients had no subependymal nodules or nodules that were not “near the foramen of Monroe”. It is essential that these factors be defined in a case and control study. For what constitutes proximity to the foramen. The authors were apparently not blinded at the point when they selected which patients had lesions near to the foramen and therefore there is an obvious issue of potential selection bias.

The consequence of excluding these patients may have been that false significance is given to their results. The data they present are fragile. Consider, for example, the consequence of introducing from these 36 non-selected patients a hypothetical single case that had a family history of tuberous sclerosis complex and a subependymal nodule which enhanced with gadolinium. The effect would be to remove the stated statistical significance (using Fisher’s exact tests) between the outcome and both of these explanatory variables.

Identifying the risk factors that can tell us why subependymal lesions will become invasive is important. As subependymal nodules and SEGAs seem to be histologically identical it is unlikely that pathologists will provide an answer. The study of Nabnout et al4 suggests some new hypotheses but does not replace others. However, the definitive answer will not be provided by studies of selected samples but by follow up of a population based sample of patients with tuberous sclerosis complex. In the absence of such a study we would be cautious about implementing screening programmes based on what may be misleading criteria.

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Atypical form of amyotrophic lateral sclerosis: a new term to define a previously well known form of ALS

We read with interest the article by Sasaki et al5 concerning the atypical form of amyotrophic lateral sclerosis (ALS). The pattern of muscular atrophy in these patients differed from that of typical ALS in that severe muscle involvement was confined to the upper limbs, predominantly the proximal portion and shoulder girdle, sparing the face and the legs until late in the disease’s course or until the terminal stage.

Over the past few years, we have noticed a growing interest in the renaming of this clinical form of ALS, which has its origins and predomination in the proximal muscles and upper limbs and little or no effect of either a bulbar nature or in the lower limbs. Thus Hu et al6 coined the term fascial arm syndrome, to describe a subgroup of patients affected by ALS that predominantly showed signs of lower motor neuron disease in the upper limbs, without significant functional involvement of other regions on clinical presentation. This subgroup of patients was clinically characterised by the display of progressive atrophy and weakness affecting the proximal muscles in the upper limb muscles in a more or less symmetric manner.

Recently, along these lines, Kats et al7 described a series of patients affected by an adult onset motor neuron disorder restricted to the upper limbs, with severe proximal and varying degrees of distal involvement, calling it amyotrophic brachial diplagia syndrome. Other terms used in the past to refer to this form of ALS have been danging arm syndrome, suspended form, or orangutan sign, dead arm sign, bibrachial palsy, rizomelic amyotrophy, and the idea of naming it a distinctive phenotype of a neurogenic
“man-in-the-barrel” syndrome has even been suggested.

Probably all these terms used to define this variation of ALS are synonyms for an older, well-known condition, the scapulopelvisal form, or the chronic anterior poliomyelitis reported by Vulpian in 1886 and known in Franco-German literature as Vulpin-Bernhardt’s form of ALS.

At certain stages of the disease’s clinical course, it is probably difficult to differentiate it from progressive muscular atrophy (PMA). Some authors have said that PMA with late onset scapulopelvisal distribution (over 45 years of age) generally leads to ALS as a matter of course.1

Be that as it may, the truth is that this atypical form of amyotrophic lateral sclerosis behaves differently from typical ALS. The comparative study with the rest of the ALS group supplied important clinical findings, such as little or no functional impairment of the bulbar muscles or legs. Hu et al also made four important statistical discoveries.

(1) The prevalence of this form of ALS constituted 10% of the ALS group as a whole (p = 0.05). (2) The age of onset of this form was similar to the rest of ALS. (3) There was a clear predominance among men (the male/female ratio was 9:1 in this form, compared with 1.5:1 in the total ALS group). (4) There was a lower mortality (a median survival of 57 months compared with 39 months in the ALS group).

Some of these patients have a long ALS clinical course, in that they usually preserve their ability to walk even for many years after the onset of symptoms.

On a personal level, we also note two findings characteristic of these patients. In the initial stages of the illness, there is no effect on the diaphragm and the respiratory muscle failure occurs much later than in the typical form of ALS. This can be seen in the follow-up of the results obtained in the respiratory function tests (PVC, PImax, and PEmax).

We do not know the reason for either the characteristic distribution of weakness or muscle atrophy. A meticulous study shows that there is an atrophy of the deltoids (supra and infraespinatus) and a loss of strength in the external rotation of the shoulder (infraespinatus, supraspinatus, and teres minor). As a consequence, the upper limbs adopt a characteristic position, with the shoulders slumped, and the arms, forearms, and hands in pronation.

The atrophy and weakness of the infraespinatus and the supraspinatus, that act as an active ligament in scapulohumeral articulation, would explain the presence of subluxation of the shoulder joints in these patients.

Finally, we are in complete agreement that the atypical form of cervical spondylosis and ALS can cause difficulty in diagnosis. The problem lies in the fact that cervical spondylosis is a common condition. It is found in 83.5% of men and 80.7% of women over the age of 55. The faster progressive deterioration of the symptoms, the appearance of bulbar signs, and the absence of sensory symptoms and signs would favour the diagnosis of ALS.1

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Sasaki replies:

We thank Gmez et al for their interest in our article concerning the atypical form of amyotrophic lateral sclerosis (ALS).1

Over many years, several researchers have recognised this peculiar distribution of muscle atrophy in clinical practice. The clinical manifestations consist of the muscular atrophy confined to the chest wall and arms (proximally dominant), absence of deep tendon reflex in the arms, almost normal deep tendon reflex in the legs, and subluxation of the shoulder joints. Some patients progress to bulbar involvement. As Gmez et al cite, many terms have been coined to describe this peculiar pattern of the muscular atrophy such as flail arm, oragn utan sign, dead arm sign, and flail arm syndrome. Isolated dysarthria was first seen in an atypical form of ALS reported by Vulpian in 1886 and known as Vulpian-Bernhardt’s form of ALS. This can be seen in the follow-up of the results obtained in the respiratory function tests (PVC, PImax, and PEmax).

We do not know the reason for either the characteristic distribution of weakness or muscle atrophy. A meticulous study shows that there is an atrophy of the deltoid muscles (supra and infraespinatus) and a loss of strength in the external rotation of the shoulder (infraespinatus, supraspinatus, and teres minor). As a consequence, the upper limbs adopt a characteristic appearance, with the shoulders slumped, and the arms, forearms, and hands in pronation.

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Isolated dysarthria

We read with interest the article by Urban et al. Using transcranial magnetic stimulation, the authors demonstrated electrophysiological evidence for a central monoparesis of the tongue in patients with isolated dysarthria from stroke.2 As in their patients transcranial magnetic stimulation induced absent or delayed corticofugal responses at the tongue, the authors ascribed isolated dysarthria to interruption of the corticobulbar pathway. On the whole our results are plausible, but we would like to comment on the underlying mechanism of isolated dysarthria.

As in the case of isolated dysarthria reported by Urban et al, all of our patients with isolated dysarthria had lacunar infarctions involving the internal capsule and corona radiata.3 Measurement of cerebral blood flow with IMP-SPECT in these patients disclosed frontal cortical hypoperfusion, particularly in the anterior opercular and medial frontal regions. Anterior opercular lesions produce facio-pharyngo-glosso-masticatory paresis (anterior opercular syndrome), and damage to the medial frontal regions, including the supplementary motor area, causes speech expression disorders. White matter lesions can disrupt afferent and efferent fibre connections in motor speech areas, resulting in dysfunction of these cortices.4 Therefore, we postulated that isolated dysarthria results from interruption of corticobulbar networks indispensable for speech output, involving the thalamocortical and corticostriatal fibres as well as the corticobulbar fibres. In fact, lacunar infarctions around the internal capsule-corona radiata are likely to underlie these ascending and descending projections.5

To assess corticopontocerebellar tract function, Urban et al investigated cerebellar blood flow in patients with isolated dysarthria using HMPAO-SPECT. We read with interest their observations that included the corticopontocerebellar tract is preserved in isolated dysarthria because of no evidence for cerebellar diaschisis on SPECT. Their SPECT findings on cerebellar blood flow were similar to our results. However, we wonder whether cerebral cortical blood flow was preserved in their patients, because our SPECT study suggested frontal cortical dysfunction as an underlying mechanism of isolated dysarthria. Vocal paresis was clinically evident in three of seven patients reported by Urban et al and in two of 12 by us. This indicates that isolated dysarthria originates in incoordination of multiple organs necessary for speech production as well as a cortical dysfunction.6 Although interruption of the corticobulbar pathways is a likely cause of isolated dysarthria, it should be borne in mind that damage to other descending and ascending projections may contribute to isolated dysarthria.7

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Intracortical inhibition and facilitation are very important in paired magnetic stimulation. The results strongly depend on the intensities of both a conditioning and a test stimulus. Especially, the intensity of the conditioning stimulus is critical. We may have to take CAG repeat number into consideration in comparisons. Unfortunately, however, we have no way to do such comparisons between these two studies. We could say, at least, that the intracortical inhibition was normal even at the same stage of the disease as that of the patients of Abbruzzese et al., if studied with our method.

We also consider that methodological differences are very important in paired magnetic stimulation. The results strongly depend on the intensities of both a conditioning and a test stimulus. Especially, the intensity of the conditioning stimulus is critical. We may have to take CAG repeat number into consideration in comparisons. Unfortunately, however, we have no way to do such comparisons between these two studies. We could say, at least, that the intracortical inhibition was normal even at the same stage of the disease as that of the patients of Abbruzzese et al., if studied with our method.

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Such a methodological problem is inherent in human studies because we have no direct way of detecting the threshold of the motor cortex. Our two results must be true. We may have two completely different interpretations of these results. (1) The intracortical inhibition is normal in Huntington's disease. Abbruzzese et al showed the reduced inhibition because they used a high intensity conditioning stimulus with which the degree of the
intracortical inhibition is often decreased even in normal subjects. The 80% of the threshold for relaxed muscles must correspond to different values relative to the threshold for active muscles in patients from that in normal subjects. (2) The intracortical inhibition is determined by the state of the patient’s disease. This slight abnormality could not be detected with their method but not with ours because their method has better sensitivity in detecting an abnormality than ours. Whichsoever is true, the intracortical inhibition must be normal or slightly disturbed in Huntington’s disease.

Critical closing pressure: a valid concept?

Czosnyka et al recently published a study investigating the clinical significance of critical closing pressure (CCP) estimates in patients with head injury. We see problems both with the theoretical foundation of their CCP concept and with the interpretation of their results. Firstly, the physiological meaning of both formulae of CCP presented (CCP1 and CCP2, respectively) is questionable. The implication of both presented equations is that the instantaneous value of cerebral blood flow velocity (FV(t)) at a given moment t is equal to arterial blood pressure at the given time (ABP(t)) minus CCP divided by cerebrovascular resistance (CVR): 

\[
FV(t) = \left(\frac{ABP(t) - CCP}{CVR}\right)
\]

At the time of systolic and diastolic pressure waves (ABP, ABPd), respectively, it follows that systolic and diastolic pressure (FVs, FVd) should be equal to (ABP-CCP)/CVR and (ABPd-CCP)/CVR, respectively. However, it is evident that the vascular resistance valid for the static pressure/flow connection (CVR0, concerning mean pressures and flows) is different from and is in general much higher than resistances determining dynamic pressure/flow relations (CVR1) as in the case of pulsatile pressure. Therefore, equation 1 cannot be applied to describe dynamic flow. This can best be illustrated using the frequency domain approach (ABP=mean pressure; FV=mean flow velocity; A1=amplitude of the pulsatile pressure wave; F1=amplitude of the pulsatile flow wave): 

\[
FV = \left(\frac{ABP - CCP}{CVR}\right)
\]

(2) Inserting equations 2 and 3 into the frequency domain equation for CCP2 of the authors CCP2=ABP−A1/F1×FV

leads to 

\[
CCP2 = ABP - CVR1/CRV0×(ABP - CCP) = ABP - CVR1/CRV0 + CVR1/CRV0
\]

Thus, CCP2 is only in the case of CVR1=CVR0 equal to CCP. Under the more realistic assumption that CVR1 is equal to about half of CVR0 it follows for CCP2: 

\[
CCP2=0.5ABP+0.5CCP
\]

With decreasing CVR1/CVR0 ratios, CCP2 becomes more and more dependent on ABP and independent of CCP. In any case, without exact knowledge of the CVR1/CRV0 ratio, equation 4 is useless for a valid CCP calculation.

The second criticism concerns the correlation of the calculated CCP values with mean ABP found by the authors \((r=0.5, p<0.05)\). According to the original idea of Burton, CCP represents a certain mean ABP value below which small vessels begin to collapse. CCP should, therefore, be a constant value independent of the actual ABP. On the other hand, this significant correlation can be explained by our equation 5, again indicating the missing physiological basis of the CCP concept of the authors.

Thirdly, it seems doubtful that CCP could be estimated using pressure and flow values from ABP ranges clearly above CCP and flow values clearly above zero flow, respectively. As long as small vessels do not collapse (ABP>CCP) it is not possible to decide whether their actual wall tension is determined more by transmural pressure or by active vascular constriction. However, the relative contribution of both effects is critical for the limit of CCP.

Finally, I would be interested in the authors’ explanation of negative diastolic flow values as seen in Doppler spectra of arteries with a high vascular resistance (peripheral arteries, middle cerebral artery during strong hypocapnia). In the case of ABP<CCP and a small vessel collapse according to the model of the authors, CVR should increase towards \(FV\) and FV towards zero (equation 1). Negative flow values could, consequently, not occur.

I suggest that the relation between pulsatile pressure and flow should be better described using the concept of different static and dynamic resistances (CVR0 and CVR1). The driving pressure of the mean flow is more accurately given by cerebral perfusion pressure (CPP=ABP-ICP) than by ABP-CCP. Therefore, equation 2 changes to

\[
FV = \left(\frac{ABP - ICP}{CVR0}\right)
\]

and equation 5 to CCP2=ABP-CVR1/CRV0×(ABP-CCP) = ABP-CVR1/CRV0 + CRV1/CRV0 (equation 7). Equation 7 explains well the positive correlations found between CCP2 and ABP and between CCP2 and ICP, respectively, without assuming a connection between CCP and Burton’s concept of “critical closing pressure”.

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Czosnyka et al reply:

We thank Diehl very much for the interesting letter provoking some mathematical considerations about cerebral haemodynamics. We need to emphasise that our primary interest was to investigate Burton’s hypothesis in patients with head injury that critical closing pressure (CCP) may be represented by a sum of intracranial pressure (ICP) and the tension in the arterial walls. CCP=ICP+active tension of arterial walls Aaslid proposed the mathematical formula taken for calculations:

\[
CCP=ABP+ABPpp/FVpp/ABPpp+FFVpp
\]

(5)

where ABP and FV are mean values of arterial pressure and MCA flow velocity, ABPs and FVs are systolic values, ABPpp and FFVpp are peak to peak amplitudes.). A graphical interpretation of this formula has been given in fig 1. CCP is an x intercept point of linear regression between subsequent systolic and diastolic values recorded within 6 second intervals of flow velocity (along y axis) and arterial pressure (along x axis).

In fact, the formula proposed by Michel et al is very similar. The only difference is that instead of the original waveforms of FV and ABP, first (fundamental) harmonic components were taken for the same graphical construction—that is:

\[
CCP=ABP−A1/F1×FV
\]

In our paper we confirmed empirically that both CCP1 and CCP2 produced the same values in a group of patients with head injury, therefore the mathematical consideration mentioned by Diehl (equations 1–5) cannot contain an error!

First of all we cannot see how equation (1) from Diehl’s letter can be derived from any of our formulae. Everyone who has tried to plot momentary values from ABP pulse waveform against momentary values of FV waveform knows that it never plots a straight line (as equation (1) implies). We believe “clouds” of systolic and diastolic values of ABP and FV waveforms (fig 1 in’ one can rather see an ellipsoidal shape which is very seldom regular enough to be approximated by a straight section. The equation (1) in Diehl’s letter is not correct. In fact, CVR is a frequency dependent variable (represents vascular impedance) and if a linear theory can be applied, division in (1) should be substituted by a convolution with an inverse Fourier transform of “cerebrovascular admittance”.

Definition of CVR0 as FV/(ABP-CCP) is completely artificial and lacks a physiological basis. It is rather taken from the geometrical interpretation of figure 1 in’ one. In our material equivalent of parameter CVR0 (as defined by Diehl) is 1.007 (SD 0.31) and CVR1 0.972 (SD 0.29), the differences are not statistically significant. Therefore, the suggestion that the CVR1/CR0 ratio is 0.5 is not correct. Real CR0 should be calculated as (ABP−ICP)/FV. We fully agree that equation (5) proposed by Diehl is “useless for valid CCP calculation”. We have not used it and have never suggested anyone could do so.

The second criticism was that our CCP positively correlated with ABP. It is an obvious truism. When ABP decreases, vasodilatation occurs and arterial wall tension decreases. Therefore presuming ICP was constant, CCP should decrease. A rather weak (though significant) correlation suggests that not all of our patients were equal, ICP pressure reactive or ICP was not always constant.

The final issue concerning negative flow velocities is a trap Diehl has prepared for himself. We never suggested that any factor interpretable as cerebrovascular resistance (CVR0 or CVR1) should be involved in the concept of critical closing pressure. From the definition, closing is a strongly non-linear phenomenon, therefore applying linear theory here is very
risky. How risky—we can see from Dieth's letter. Cerebrovascular resistance certainly never increases to infinity, only after death.

We fully agree with the considerations regarding equations (6) and (7). CCP can be risky. How risky—we can see from Diehl's letter. Cerebrovascular resistance certainly never increases to infinity, only after death.

Finally, we are truly obliged to Diehl for an opportunity to have this interesting discussion.

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219–21.

High frequency stimulation of the subthalamic nucleus and levodopa induced dyskinesias in Parkinson's disease

Reduction in the neuronal activity of the sub-thalamic nucleus leading to diminished excita-tion of the globus pallidum internum is associated with chorea-ballism in monkeys.1 Levodopa induced dyskinesias are currently thought to share a similar pathophysiology2 but recent findings also suggest that abnor-mal patterns of neuronal firing in the globus pallidum internum may be as relevant.3 Data from both parkinsonian monkeys and patients with Parkinson's disease submitted to lesion4 or functional blockade of the sub-thalamic nucleus5 are in keeping with such a general principle, but the threshold to induce dyskinesias in the parkinsonian state is higher than in intact animals.6 The case recently described by Figueiras-Mendez et al is extremely interesting as it suggests that func-tional inhibition of the subthalamic nucleus by high frequency stimulation blocks levodopa induced dyskinesias. This is clearly at odds with the current pathophysiological model of the basal ganglia.7 Thus, the finding of Figueiras-Mendez et al rises the intriguing possibility that dyskinesias depend or are mediated by neuronal firing in a given region of the subthalamic nucleus, which was blocked by high frequency stimulation. Measurement of afferent synaptic activity by the technique of 2-deoxyx glucose (2-DG) uptake showed an increment in the subthala-mic coefficients describing properties of increased inhibition from the globus pallidum exter-num), particularly in the ventromedial tip of the nucleus. This contrasts with the findings in monkeys with chorea induced by pharmac-co logical blockade of the globus pallidum extraseptal exter-num, in which 2-DG uptake was maxim-al in the dorsolateral portion of the subthal-a mic nucleus, where the sensorimotor region lies. A recent anatomical study8 also showed that the cortical-subthalamic neurones con-nection is somatotopically segregated, so that fibres from the supplementary motor area project to the most medial portion and fibres from the primary and premotor areas termi-nate in the lateral region of the subthalamic nucleus.9 All this heterogeneity may have pathophysiological relevance, describing one aspect of which could be the findings in the patient reported by Figueiras-Mendez et al.10 However, before the findings of this case may be used to sustain an hypothesis on the role of the subthalamic nucleus in the origin of levodopa induced dyskinesias, there is a cru- cial issue to resolve—namely, the location of the tip of the stimulation electrode.

There are several points leading us to question the actual site of action of the electro-de: (1) Stimulation of the subthalamic nucleus in Parkinson's disease has been asso-ciated with the production of dyskinesias only with relief by levodopa intake.11 Moreover, Benabid et al who pioneered this technique, consider the induction of dyskine-sias by high frequency stimulation of the sub-thalamic nucleus as a good indicator of a very positive response to stimulation.12 There following to the thalamus from the globus pallidum internum are placed dorsocaudally to the subthalamic nucleus and could be blocked by high frequency stimulation. (2) When the record-ing electrode was placed ventromedially caudal to the subthalamic nucleus in sagittal planes 11 mm or less, neuronal activity is characterised by action potentials of large amplitudes (0.5–1 mV) with low background activity, tonically firing neurons, and absent sensori-motor responses (“driving”). All these char-acteristics seem to be present in the patient discussed here. Neuronal activity in the sensorimotor region of the subthalamic nucleus is different from the above but on occasions the distinction may not be easy. Accordingly, it is very important to doc-u-ment in more detail the findings in the case of Figueiras-Mendez et al.10 Ideally, we would like to see the trajectory and length of the differ-ent recording tracks, the effects of micro-stimulation, and the post-surgical MRI with measurement of the tip of the electrodes. If, as assumed, the subthalamic nucleus was indeed correctly targeted in this patient, the pathophysiology of the basal gan-glia will need to be revisited.

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Nitric oxide in acute ischemic stroke

The pivotal role of nitric oxide (NO) in cerebral ischemia has been elegantly highlighted in the recent editorial by O’Mahony and Kendall. A. Although studies of neuroprotective agents have been largely disappointing, pharmaceutical manipulation of NO may represent a novel means of protecting the brain from ischemic insult. One area not discussed in this context is the neuroprotective effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or “statins” in cerebral ischemia. Preliminary studies have shown that statins modulate brain nitric oxide synthase activity and neuronal NO synthase activity in a neuroprotective manner. Data from a murine model of ischemic stroke demonstrate that prophylactic statin therapy reduces infarct size by about 30% and improves neurological outcome in normocholesterolemic animals. In this investigation, statin therapy directly up regulated endothelial NO in the brain without altering expression of neuronal NO. Recent findings also suggest that statin therapy inhibits the production of inducible NO. Lovastatin has been shown to inhibit cytokine mediated upregulation of inducible NO and production of NO in rat astrocytes and macrophages, and this inhibition may represent a new mechanism for suppressing inflammatory responses that accompany ischemia. Most interestingly, these preliminary findings suggest that statin therapy may modify the response of peripheral and cerebral vasculature. The Therapeutic Neuroprotective Side of Statins (TRAPP) study will help clarify their role in human cerebrovascular disease.

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O’Mahony replies:

The comments of Vaughan and Delanty draw attention to the evidence that statin therapy up regulates the production of NO without affecting neuronal NO. Their contention is that statin therapy may be neuroprotective. Statistical analysis and meta-analysis may already prevent strokes and reduce infarct size when given as prophylactic therapy in at risk persons. However, our editorial article was not intended to discuss the wide variety of pharmacological agents that may have favourable effects on endothelial NO as stroke preventive therapy. Rather, it is focused on the possible ways of inhibiting neuronal NO and inducible NO methods mediated nitric oxide release after the event of acute stroke. At present, there is no evidence indicating that acute administration of statins in animal models of ischemic stroke is neuroprotective. Their point about statins and endothelial NO is interesting, but not relevant to neuroprotective therapy in acute stroke.

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BOOK REVIEWS


That neuroimmunology has come of age is demonstrated by the profusion of volumes published on the subject in recent years. This volume focuses on the central nervous system, and aims to satisfy the curiosity of both the clinician faced with a diagnostic conundrum and the experimental immunologist inquiring into the clinical relevance of his findings. At first sight it seems improbable that both of these goals might be achieved in one volume; this book however, succeeds admirably in what it sets out to do, as much as a result of its literary style as its content.

The intrusive authorial voice fell into disfavour in literary circles around the turn of the century because it was thought that calling attention to the act of narrating might detract from realistic illusion, so reducing the emotional intensity of what was being represented. It is a device much favoured by postmodern writers, who expose the nature of fictional constructs. The intrusive medical author never dropped out of fashion, although in these days of evidence based prejudice, authorial omnipotence might be considered suspect. The authors of this volume are intrusive in a guiding conversational manner that makes this book by far the most readable of the neuroimmunological texts. The book opens with a highly accessible chapter on immune responses in the nervous system. There follows a chapter that integrates the neurobiology of multiple sclerosis with contemporary issues of aetiolog, cell injury, and repair. Next, a chapter on inflammatory demyelinating disease in the examination of syndromes of isolated demyelination, acute disseminated encephalomyelitis and allied conditions, and some of the syndromes of demyelination that are now accepted as part of the range of multiple sclerosis. The chapters on demyelinating disease are drawn to a close by a discussion of existing and experimental therapies for multiple sclerosis.

The book continues with chapters on paraneoplastic disorders of the CNS, stiff man syndrome, neurological complications of...
connective tissue disorders, organ specific autoimmune, sarcoidosis, and cerebral vasculitis.

Each chapter is an appropriate length and well referenced; the wood is always clearly visible between the trees. This book is sufficiently readable and small to be recommended as a holiday reading. Its only drawback is that in making erudition so readily available, one risks being outshined yet again by one's registrar.

JON SUSSMAN

Alzheimer's Disease—from Basic Research to Clinical Applications. Edited by HERMANN J GERTZ and THOMAS ARENDT.

As Alzheimer's disease becomes of increasing importance to society, basic science research in this field needs to provide the building blocks for therapeutic interventions and accurate diagnosis. This publication is a collection of papers presented at an international Alzheimer's disease research meeting in Leipzig in 1997. This conference aimed to bring together both clinical and basic science disciplines and is reflected in the papers selected for this book. There are 31 papers included, covering topics from early symptomatology and cognitive features to immunobiology and theoretical neuronal treatment strategies. The contributors to this book are some of the most authoritative in their field, predominantly based in Europe.

Covering all aspects of Alzheimer's disease, the book is divided into five sections covering the historical concepts of vascular and Alzheimer's dementias, the arguments for a pure vascular dementia, the role of Alzheimer's disease in the genesis of dementia after stroke, the connection of white matter changes on neuroimaging to dementia, and finally a short section examining practical questions such as the management of stroke in patients with dementia.

Although common conditions are often their own right, stroke and Alzheimer's disease do seem to cross paths more often than would be expected by chance alone, and more often than can be explained by the presence of unmasking angiopathy and recurrent lobar haemorrhages. Perhaps common genetic factors are responsible and here the apoE alleles are discussed. The comprehensive section on deep white matter lesions seeks to explain the connection further—and convinces the reader that there is still a lot which is not well understood. It is in this section particularly that illustrations are greatly missed. Brief mention is made of other conditions which may produce white matter changes and dementia such as CADASIL, cerebral lupus, and the primary antiphospholipid syndrome.

Some typographical errors and mistranslations detract a little from a book which seems unlikely to appeal to most neurologists, although it will no doubt be a source of reference to those working in the field of cognitive disorders, particularly vascular dementias.

PETER MARTIN

Healing Stories—Narrative in Psychiatry and Psychotherapy. Edited by GLENN ROBERTS and JEREMY HOLMES.

Evolutionary biologists would probably tell us that the enchantment of stories is due to survival having been dependent on the passing of oral culture from one generation to the next. Information put in narrative form not only delights, but is easily recalled. Stories also construct meaning through the sharing of observation, inference, motive, and consequence in a fashion that informs future action. Our experience of the world is constructed around such narratives. They define us as individuals, family members, professionals, and cultural groups.

This book is a series of essays on psychotherapy, psychiatry, and also medicine that sees the awareness and use of narrative in clinical practice as a construct that can both...

*Childhood Epilepsies and Brain Development* is the fruit of a symposium held in 1997 to try and bridge the chasm between those working in the clinic or at the bedside and those in the laboratory. Both groups must collaborate and communicate to improve the management of children (and adult patients) with epilepsy.

The book is essentially a collection of monographs of heterogeneous content and style and the result, perhaps not surprisingly, is that some of the component parts are better than the whole (the chapters) are better than the whole (the book). This disclaimer seems to have allowed them to mix evidence and opinion, limit references, and confuse the reader regarding the level of evidence. A pity, as the authors, with special expertise in this important area, have made a good start in putting together different aspects of the care of the woman with epilepsy in a practical book that is of direct interest and relevant to neurologists, obstetricians, general practitioners, midwives, psychologists, social workers, and others.

Moving on from the general to the particular, the text, although expansive in parts, glosses over some important points. Examples include (a) which oral vitamin K preparations are considered safe in pregnancy (phytomenadione), (b) differential efficacy of various antiepileptic drugs in different syndromes versus side effect and teratogenicity profile, (c) more information on the utilization of available evidence to support the statement “no monotherapy human abnormality reported” with certain new antiepileptic drugs in pregnancy, (d) the need to consider pregnancy prevention well before the menopause (and not only with enzyme inducing drugs such as valproate which has also been implicated), (e) discussion of differences (and available formulations) between synthetic and natural progesterone, (f) strand of pregnancy when various malformations are detectable on scanning, and (g) time to closure of the neural tube (different from the 21-56 days they quoted as the “most sensitive time of the fetus to the induction of malformations by exogenous agents.”).

Despite these comments (made with an eye on the next edition) I would recommend this book to all those involved in the care of women with epilepsy.


Difficult clinical problems in psychiatry come in many forms. Diagnosis often causes difficulty, particularly in cases which demand some assessment of the role of physical illness in symptom formation. Perhaps for most psychiatrists practising in community settings risk assessment comes high on their list of concerns.

Unsurprisingly, given the psychopharmacological expertise of the editors, this book is particularly interested in treatment resistance. The first 6 chapters give excellent reviews of the management of clinically relevant topics—for example, refractory schizophrenia or the difficult panic patient. The emphasis is much on pharmacological management.

The second half of the book is more of a mixed bag, both in terms of the areas covered and the quality of the chapters. Some chapters covering all aspects of the assessment and management of anorexia nervosa and chronic fatigue are followed by a thorough review of the pharmacological management of substance misuse. Then come two weak chapters on behavioural disturbances in old age and the violent patient in the community.

This last chapter will be of particular interest to community psychiatrists who are likely to find it valuable. I would recommend because some aspects of the practical management of violence are missing—for example, a documented risk-benefit analysis, good failsafe communication, or deciding when to detain. One of the last chapters is a very good account of the management of hyperactivity in childhood, with good practical advice on the use of methylphenidate.

Apart from the chapters on chronic fatigue and the treatment of tardive dyskinesia there is little in this book which is of immediate interest to neurologists. However general psychiatrists wishing to improve their prescribing skills will find this book useful.


In a small accessible and easily digestible volume, the authors address a clinically important field. Faced with slim evidence on which to base clinical recommendations, they acknowledge that their very useful management advice “has often had to be based on practical clinical experience rather than the results of clinical trials or formal research…” This disclaimer seems to have allowed them to mix evidence and opinion, limit references, and confuse the reader regarding the level of evidence. A pity, as the authors, with special expertise in this important area, have made a good start in putting together different aspects of the care of the woman with epilepsy in a practical book that is of direct interest and relevant to neurologists, obstetricians, general practitioners, midwives, psychologists, social workers, and others.

The rest of this book is of variable quality. There is a rather prosaic essay on gender issues, and there is repetition in various chapters concerning attachment theory, a useful but over worked paradigm. However, there are two very fine accounts of narrative in psychotherapy by James Phillips and Jeremy Holmes.


The Maudsley prescribing guidelines are produced each year for a local readership, but this, the fifth edition, is the first to go public. The authors and principal contributors, a mixture of pharmacists and psychiatrists with an interest and background in clinical psychopharmacology, are to be complimented on producing a guide of manageable size and ready accessibility.

The book is divided into sections dealing with the treatment of broad groups of clinical disorders—for example, psychosis—special patient populations—for example, elderly people, with further sections on the management of emergencies and the adverse effects of psychotropic drugs. Much of the information is laid out in tabular form. It could become an indispensable resource for a busy on call inpatient house officer (the dimensions would fit comfortably into the pocket of a clinical white coat, were they still to be worn) but more senior clinicians will find plenty of use for it in the clinic. It does not aim at great erudition, but provides a useful list of references.

There are a few cavils. The section on treatment of anxiety is skimpy (one and a half pages) compared with say the treatment of affective illness (22 pages) or schizophrenia (20 pages). The brevity is only explained by the undeveloped state of that particular area of psychopharmacology. Sections on indications to and contra indications for lumbar puncture and indications for EEG seem to have been displaced from some other primer for busy junior doctors. There is no index.

These quibbles apart, prescribing guidelines can be wholeheartedly recommended.


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Spinal accessory neuropathy and internal jugular thrombosis after carotid endarterectomy

GEORGE WOODWARD and RAM VENKATESH

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