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 Antiepileptic drugs were withdrawn to facilitate seizure recording.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.

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 hyperfusion 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 interest of regions (ROIs) were measured on coronal and axial slices containing basal ganglia (BG), mesial (MT), and lateral temporal lobe structures. Asymmetry index (ASI) was calculated as ((ROI focus−ROI contralateral)/ROI focus+ROI contralateral)×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% (-6.46476 to -1.65289); over the right LT was +116.7% (1.07927 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 -3.8% (13.14217 to 12.64158); over right LT was +178.6% (10.4696 to 18.70057); and over left BG was +155.9% (-5.8556 to 3.27522).

Postictal psychosis is a distinct clinical event 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 and the onset of psychosis can be identified by abrupt withdrawal of antiepileptic drugs. The cluster occurs in patients with poor drug compliance or during video EEG telemetry studies when antiepileptic medications are withdrawn purposefully. The clinical course of postictal psychosis is usually benign and predictable. In our patients, the duration of psychotic disturbances lasted from a few days to several weeks, which is in keeping with the good prognosis. Antipsychotic drugs, such as haloperidol and fluphenazine are usually prescribed.

The underlying mechanism of postictal psychosis is unknown. Postictal cerebral SPECT was performed on two right gyri recti and one cerebellar tonsil were identified, respectively. Operations for ruptured aneurysms of the anterior communicating artery or for Arnold Chiari disease.

Immunohistochemical evaluations were performed on 5 μm thick cryostat sections using a protocol reported previously. Owing to the limited amount of available material, only in a few cases was some fresh tissue retained to allow western blots. Distribution of FN and TN isoforms was investigated using three monoclonal antibodies (mAbs) or two Ab fragments, obtained using display technology, respectively. These Abs, prepared in our laboratory, were found to work on fresh frozen material. According to the previous characterisations the BC-1 mAb and the TN-11 Ab fragments are specific for isoforms occurring almost exclusively in fetal tissues and in tumours, with the recognised TN isoform being typically associated with anaplastic gliomas (table). The antibodies were blocked using the specific antigens. 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 repeats 7B–8–9. For the Ab 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 EGF-like repeats were used respectively.

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 mAb BC-1. Staining was also observed in the vascular walls of fetal vessels as shown by intense staining of the vascular wall surrounding the angiomatic nidus. In all cases the wall of several vessels exhibited intense staining with the use of the TN-11 Ab fragment. Using the BC-1 mAb some of these vessels exhibited some staining (figure). In the control specimens (brain and cerebellum) both the FN isoform containing the ED-B sequence (ED-B+FN) and the type III repeat C TN isoform were absent, despite the widespread distribution of total FN and TN in the vascular walls.
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 hypothyroidism in the United Kingdom, it is likely that Hashimoto's encephalopathy has 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 of 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 the police. His business had been in decline for several months, and his family had noticed uncharacteristic emotional lability. In the weeks preceding admission he had experienced delusions and hallucinations, and exhibited uncharacteristic behaviour. He had reported a vision of the crucifixion, and hearing the voice of his dead mother. He claimed that his house was occupied by the devil, drove around aimlessly in his car, and appeared constantly fearful and withdrawn. On the day of admission he had made a bonfire in the garden and burned his wife's clothes, family photographs, furniture, and business papers.

When his wife and son tried to intervene he

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became aggressive and threatened them with a saw. The general practitioner was called and surmised a possible psychotic or an acute depressive illness. 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 psychotic 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 the 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, suggesting a predominantly “dysexecutive” pattern. CT and EEG were both normal, suggesting a predominantly “dysexecutive” pattern. CT and EEG were both normal, suggesting a predominantly “dysexecutive” pattern.

### Laboratory and neuropsychological results at presentation (A) and at 12 month follow up (B)

<table>
<thead>
<tr>
<th>Laboratory (units)</th>
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<th>B</th>
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<tbody>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
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</tr>
<tr>
<td>Urea and electrolytes (mmol/l)</td>
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<td>Normal</td>
</tr>
<tr>
<td>Liver function tests (normal range)</td>
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<td>Normal</td>
</tr>
<tr>
<td>Anti-thyroid microsomal antibody titre</td>
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<tr>
<td>Free T4 (pmol/l)</td>
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<td>Not tested</td>
</tr>
<tr>
<td>Antithyroid microsomal antibody titre</td>
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<td>25/30</td>
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<tr>
<td>Psychometric (normal/abnormal predicted range):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folstein MMSE (&gt;24)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>NART IQ (verbal)</td>
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<td>10</td>
</tr>
<tr>
<td>WAIS-R (performance)</td>
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<td>14</td>
</tr>
<tr>
<td>WAIS-R (verbal)</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>FAS verbal fluency (&gt;30)</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Cognitive estimates test (&lt;6)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Digit span forwards (&gt;5)</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Rey-Osterreith complex figure (copy) (30%)</td>
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<tr>
<td>Rey-Osterreith complex figure (recall) (30%)</td>
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</table>

At 6 month follow up the patient had developed florid psychotic phenomena, which again brought forth the “ceiling was falling” and the 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.

### Alien hand sign in Creutzfeldt-Jakob disease

The clinical picture of Creutzfeldt-Jakob disease (CJD) includes various movement disorders such as myoclonus, parkinsonism, and 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. Voluntary movements occur in above 90% of the patients in the course of the disease, the most common being myoclonus. Other movement disorders range from tremor to severe dystonia, and hemiballism. We report on a patient with CJD who presented with an alien hand.

Alien hand is a rare and striking phenomenon defined as “a patient’s failure to recognise the action of one of his hands as his own”. One of the patient’s hands acts as a stranger to the body and is not cooperative. Thus, there is a loss of feeling of ownership but not loss of sensation in the affected hand. Originally described in callosal tumours, the aetiology of alien hand also includes surgical callosotomy, infarction of the medial frontal cortex, occipitotemporal lobe, and balanitis, and corticobasal degeneration.

A 70 year old, right handed Jewish man born in Argentina, living in Israel for the past 20 years, was admitted to the Neurology Department. Until a month prior to admission, he was apparently healthy and helped in the accounting office of the village where he lived. His neurological illness had presented insidiously during the past month with development of gait and fine finger dyspraxia. He also manifested behavioural changes, became aggressive, and had visual hallucinations, perceiving insects and mice moving through his visual field. Often, he expressed his fear from seeing that the “ceiling was falling”, had bought a new house, and was taking thyroxine. He reported feeling “back to normal”, had bought a new house, and was taking thyroxine. He reported feeling “back to normal” and was taking thyroxine. He reported feeling “back to normal”, had bought a new house, and was taking thyroxine. He reported feeling “back to normal”, had bought a new house, and was taking thyroxine. He reported feeling “back to normal”, had bought a new house, and was taking thyroxine. He reported feeling “back to normal”, had bought a new house, and was taking thyroxine. He reported feeling “back to normal”, had bought a new house, and was taking thyroxine. He reported feeling “back to normal”, had bought a new house, and was taking thyroxine. He reported feeling “back to normal”, had bought a new house, and was taking thyroxine. He reported feeling “back to normal”, had bought a new house, and was taking thyroxine. He reported feeling “back to normal”, had bought a new house, and was taking thyroxine.
falling over him”. 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 concept, hallucinations, were disturbed by hallucinations. The attack 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 commands involving two consecutive components. Naming was preserved. Prominent dysgraphia 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 found. The patient had no cortical sensory loss.

The laboratory data including blood chemistry, hematocrit, and sedimentation rate were normal, as were folate acid, vitamin B12, concentrations, and thyroid function. Vene-
real disease research laboratory and HIV tests were negative. The cerebrospinal fluid had normal content. Brain CT showed mild cerebral atrophy. An EEG showed severe diffuse slowing at admission. Within a week, repeated EEGs showed triphasic waves with a periodic pattern of 1-1.5 Hz.

During the next 2 weeks, the patient developed multifocal myoclonic jerks. Severe dysphasia and cognitive decline were accompanied by confusion and aggression. He became grossly ataxic, and unable to walk and perform any of his daily activities even with help. Transferred to a chronic care hospital, he died five weeks later. Postmortem examination was not allowed.

This short fatal neurological disease manifested by fulminant dementia, myoclonic jerks, and extrapyramidal and cerebellar dys-
function was strongly suggestive of CJD. The periodic EEG pattern reinforced this diagnosis. Our patient’s alien hand was part of the otherwise characteristic clinical picture of CJD, but occurred early in the disease course when no myoclonic jerks were present. We are aware of only one report of alien hand in CJD. MacGowan et al. described two patients with CJD and a myoclonic alien hand syndrome. In one patient the left arm “was noted to have spontaneous movements which appeared purposeful...wandered out of her view”. In the second, the alien limb performed complex movements such as unbuttoning her blouse and removing a hair pin. Although our patient had no myoclonus or pyramidal signs when the alien hand appeared, in their patients it was associated with spontaneous and stimulus sensitive myoclonus, spastic hemiparesis, and cortical sensory loss.

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. The callosal and cortical degeneration, there are aimless movements of either hand. When a consequence of neuronal or vascular 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 cortical callosal degeneration. These authors described the alien limb as “involuntarily rising and touching the mouth and eye” (patient 1). The patient thought that she “was powerless to stop this movement” and when directed to stop responded that “she can’t”. 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, cortical degeneration, and progressive multifocal leukoencephalopathic, in which an alien hand sign has also been described, is multifocality. In cortical 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 myo-
clusus.

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

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Recurrence 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 (ESPGHAN) crit-
ria. 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 erroneously thought to be gluten free. No previous infections had been noticed. One week after the onset of these symptoms she experienced acute weak-
ness 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. Neurologi-
cal examination disclosed symmetric, pre-
dominantly distal, weakness of the legs; 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: haemoglo-
lin, erythrocytate, serum urea, nitrogen, electrolytes, creatinine, glucose, transaminase, bilirubin, immunoglobulins (Igs), lead, iron, copper, urinalysis, urinary pyrophoric, follic acid, and vitamins A, B, B₁₂, and E. Anti-
body to Campylobacter jejuni, anti-endomysial antibodies, anti-transvirus antibodies, specific and non-specific organ autoantibodies, IgA and IgG antigliada-
in antibodies (AGAs), IgA antiendomesial antibodies (EMAs), and IgA antireticulum antibodies (ARA), assayed by enzyme linked immunosorbent assay (ELISA) and immuno-
fluorescence (IF) were also negative. Lumbar puncture was not performed. Anti-
bodies against gangliosides GM₁ and GM₂ were not detected. 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 the upper limbs.

<table>
<thead>
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<th>2nd Episode</th>
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<td><strong>Peroneal</strong> $L_1$</td>
<td><strong>Tibial</strong> $L_1$</td>
</tr>
<tr>
<td>MCV (ms)</td>
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</tr>
<tr>
<td>74</td>
<td>22</td>
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<tr>
<td>DL (ms)</td>
<td>7.3</td>
</tr>
<tr>
<td>7.5</td>
<td>7.2</td>
</tr>
<tr>
<td>F wave latency (ms)</td>
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<tr>
<td>Sural $L_1$</td>
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<tr>
<td>AMP ($\mu$V)</td>
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<td>1st Episode</td>
<td>16.8</td>
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</tbody>
</table>

MVC= motor conduction velocity; DL = distal latency; CMAP = compound muscle action potential; SCV = sensory conduction velocity; AMP = amplitude; $L_1$ = left; $R_1$ = right.

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.1

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, wallerian and axonal degeneration may be caused by vasculitis, 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.1

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.

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**1 Cooke WT, Thomas Smith W. Neurological disorders associated with adult coeliac disease. Brain 1966;89:683–722.**


### Frontal release signs in older people with peripheral vascular disease

A growing body of research examining neurological aspects of clinically "silent" cerebrovascular disease suggests that neurological signs indicative of generalised organic brain damage may occur in the absence of completed stroke.1 These soft signs include primitive reflexes (frontal release signs), representing an anatomical and functional deafferentation of cortical from subcortical structures. Primitive reflexes are known to occur in a wide variety of dementias, including Alzheimer's disease2 and vascular dementia.3 It is likely that the presence of undetected cerebrovascular disease accompanying peripheral vascular disease is underestimated, as peripheral vascular disease is known to be a risk factor for transient ischaemic attacks. A study assessing 373 older patients with peripheral vascular disease found that 72 of the 144 patients who had not experienced a transient ischaemic attack at the time of interview were found to have a degree of carotid stenosis of between 60% and 99%.4

In the present study, the prevalence of primitive reflexes was examined in a sample of people with peripheral vascular disease and a non-vascular control group. Independent predictors of these reflexes were also examined in peripheral vascular disease. Both groups were drawn from the same geographical area. All were interviewed and examined outside hospital by myself. Interviewees were community residents from the catchment area of an inner city London teaching hospital.

Twenty five consecutive non-amputees on the waiting list for femoropopliteal bypass operation were compared with 25 postoperative patients who had undergone elective hip or knee replacement and a postoperative rehabilitation. All participants were aged 65 and over at the time of interview. Patients with peripheral vascular disease all had clinical and Doppler proved evidence of peripheral ischaemia. Controls were interviewed between 6 months and 1 year after their operation. Both groups had no history of stroke or transient ischaemic attack.

A more detailed description of instruments is provided elsewhere.5 All subjects were

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**1 Cooke WT, Thomas Smith W. Neurological disorders associated with adult coeliac disease. Brain 1966;89:683–722.**


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examined using a rating scale for the examination of frontal release signs (FRSS), with nine operationally defined items, each on a seven point semi-quantitative scale. The nine reflexes were paratonia and palpomental, hand grasp, foot grasp, glabellar, rooting, snout, and visual/tactile sucking reflexes. Neuropsychological measures included the assessment of frontal lobe function (traitmaking 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, wish 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 subcales 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 scores, 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, Cohen’s d effect size, 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/below 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 binary logistic regression equation using the stepwise method.

Patients with peripheral vascular disease had a higher mean score on the frontal release signs scale than controls (9.8 (SD 4.6) vs 1.7 (SD 1.0)) and a higher mean on the Mann-Whitney test for independent samples (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 (R²=0.46, 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 between neurological and cognitive sequences of coexisting cerebrovascular disease. Phillips et al found greater impairment in psychomotor speed and abstract reasoning in patients with peripheral vascular disease than age/sex matched 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 areas compared with a matched group of stroke patients.5

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 the resultant 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 Dr Willem and 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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Factitious clock drawing and constructional apraxia
A 45 year old man presented with a 1 day history of headache, possible seizures, and left sided weakness. On the day of presenta-
tion the patient’s wife had twice found him, inexcusably, on the floor. After the second such episode she brought him to hospital for evaluation. Examination disclosed a complete left hemiplegia and hemianesthesia, although muscle tone was documented to be normal and the plantar responses downgoing bilaterally. Brain CT was normal and routine blood examination was unremarkable. There were no further seizure-like episodes and the patient was transferred to this hospital 10 days later, hemiplegia unchanged, for possible angiography and further investigations.

He was an ex-smoker with hypercholesterolaemia and peripheral vascular disease which had been treated by a left femoral angioplasty 5 years earlier. The angioplasty was complicated by the occurrence of a pseudoaneurysm 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 outpatient brain MRI 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 to within 5 mm, 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 hemianop sia 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 unre-
martant.

Brain CT and MRI, CSF examination, and routine EEG were normal. Routine haematolog
cal and metabolic analyses plus erythrocyte sedimentation rate, serum lactate, pro
thrombin time, partial thromboplastin time, fasting serum glucose, HbA1c, serum igown
ty, and thyroid stimulating hormone were all within normal limits. A hypercoagulability profile was negative. A lipid profile showed mildly 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 phenytin concentration was therapeutic at 74 µmol/l. An ECG was normal.

Ophthalmological consultation and formal visual field testing demonstrated a concentric 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 and spelling errors, the second involving unusual “near miss” letter substitutions or reversals (for example, “anixety”, “excecu- tion and spelling errors, the second involving memory, as well as several atypical calcula-

A ECG was normal.

The mental status examination described above indicate beyond any doubt the non-organic nature of this patient’s left hemiplegia/hemianesthesia. His seizure-like episodes at presentation are presumed to have been non-epileptic in origin (as had been suspected during his previous admission to hospital) although this cannot be definitively proved.

The inability to copy line drawings or to draw a clock is, from a neurologist’s perspective, typically associated with parietal lobe dysfunction, usually of the non-dominant hemisphere, especially if associated with left hemispatial neglect. To our knowledge, this is the first reported case of factitious clock drawing and constructional apraxia. Bedside mental status testing also demonstrated the more common simulated deficits of impaired attention and absent three word recall. In retrospect, the severe neglect on clock drawing was perhaps “too good to be true”, especially in the light of the near normal line bisection demonstrated on the same day. The mirror image distortion of the house was also very unusual and, furthermore, the mirror reversal itself is evidence of lack of clinical neglect. The distortion of the cube, however, could easily be misinterpreted as evidence of organic constructional impairment if seen in the absence of the other relevant clinical and laboratory information.

During follow up, the patient admitted to feeling tremendous occupation related stresses, and described how he had come to both fear and detest his job. Given the clear benefit to the patient of removal from his work environment, the relapse of his symptoms just as he was scheduled for return to work after his first non-organic hemiplegic episode, and the intentionality required to feign poor clock drawing and constructional apraxia, there is much to support a diagnosis of malingering. Nevertheless, classification as a factitious disorder is at least as justifiable in view of 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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A (A) Asked to “put all the numbers on a clock and make the time ten to two”. (B) Patient’s copies (at right) of three dimensional line drawings. Top: common constructional distortion of cube. Bottom: unusual mirror image representation of house.
appropriately. Neurological examination showed contralateral gaze preference, supra-nuclear vertical gaze palsy, difficulty converging, left sided faciobrachial hemiparesis, and dense, left sided hemianaesthesia. 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 acknowledged 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 more often nearer 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 him. This was a spontaneous and lucidly recalled belief, otherwise. By this time he had a moderate hemiplegia and recognised “a little weakness,” but continued to insist that he was well and able to return to work. By the 6th week another patient more consistently acknowledged that he was weak on the left side of his body. A request for disabled housing “so that I won’t be a burden to my family” seemed to indicate an appreciation of his impaired ability to function, was being considered 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 after stroke before being 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 cheerful and optimistic. A week after the stroke he was noted to praise extravagantly the hospital food, and the nurses found him “talkative.” When he arrived on our ward 11 days after the stroke he was hyperactive, with no motor disturbances or difficulty in communication, and he was returned to the nurses’ station for closer observation. He spontaneously recalled believing that he had had a stroke, but, despite his stroke, he had significant problems with conceptual shifting (both auditory and visual). Later during his hospitalisation, processing difficulties included very poor reading ability, impaired confrontation naming, and impaired performance on a verbal task of fluency and initiation. Auditory comprehension was mildly impaired. Vocabularly scored formally in the borderline impaired range, as did abstract verbal reasoning. On tests of praxis he demonstrated a tendency to use the hand as object. Memory performances were generally intact. His initial recall of two paragraphs scored formally within the average range and after a 30 minute delay, he was able to recall most of the information initially encoded, scoring formally within the average range.

Structural brain MRI on admission to the emergency room showed a large right thalamic hemorrhage with mass effect and oedema, with oedema extending into the cerebral peduncle. The blood was susceptability consistent with deoxyhaemoglobin. Also present was increased T2 signal bilaterally in the thalami, consistent with deoxyhaemoglobin. This is a case of anosognosia of hemiplegia and mania co-occurring in a patient with a large right thalamic haemorrhage. Although anosognosia and mania are not generally thought of as occurring together, Babinski’s introduced the term anosognosia here as part of his example. In a case in which the patient, though obviously confused, was “a little overexcited,” and in a later paper he presented a case in which there was “a certain agitation, which expresses itself by exaggerated 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 Knoth emphasized that apathy is the mood more usually associated with anosognosia, 10% of his patients with anosognosia 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 hemispheric 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 disike of the left arm (other anosognosic phenomena) on the basis of euphoria. Moreover, Starkstein et al, finding that similar 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 influence one's insight. Several explanations have been proposed to explain the phenomenon of anosognosia. 7

All the models invoke dysfunction of the cerebral cortex, especially the parietal cortex. It is interesting that in this case functional MRI failed to demonstrate decreased CBV in the parietal lobe. In summary, we present a case of a patient with anosognosia and mania co-occurring with a right thalamic haemorrhage. The coexistence of mania and anosognosia may be more common than previously appreciated. The association 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 pacemaker he has had no further episodes. In cases of epileptic cardiac dysrhythmia, isolated EEG or EEG recordings may prove insufficient and prolonged simultaneous EEG/ECG monitoring may be required.

Cardiac arrhythmias subsequent to epileptic 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 restored.

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, while standing, suddenly collapse to the ground where he would remain unrousable, 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. During the period of the episode his heart rate 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 occur at least once or twice a day before he was started on phenytoin, with no benefit. Carbamazepine was added, again with minimal effect.

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

Cardiac and neurological examination was normal 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. Internally rare spikes were seen over the right frontocentrotemporal region during sleep. The onset of the episode was not witnessed and the patient was found lying on the floor, regaining consciousness at about 07:06. The event EEG showed a short run of bilateral semi-hemispheric 2–3 Hz activity at 07:04:34 (figure A), persisting for 8 seconds before being obscured by muscle and movement artefact. Twenty seconds later, 10 seconds after the 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 lasting 15 seconds (figure B). After a few seconds of bradycardia then asystolia, 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 a large amplitude generalised rhythmic <1 Hz 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 action. A series of 26 patients with 74 temporal lobe seizures in which simultaneous EEG and ECG recordings were acquired, 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 than controls (11).

It has been hypothesised that there is lateratisation with respect to central autonomic cardiac control with an increase in heart rate seen after an acute reduction of amobarbital and inactivation of the left hemisphere and a decrease in heart rate on right hemispheric inactivation. Experimental stimulation of the rostral posterior insular arthery 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 molecular basis 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 palsy 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 where respiratory failure and proximal muscle weakness were prominent features.

The patient started to have dypsnoea on exertion 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 the Norfolk Red Cross Hospital emergency patient with a coma due to CO2 narcosis (PCO2, 117.6; PO2, 64.0). Responsive 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 or other medical problems. 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 was noticed. 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 hypoactive in all limbs. The patient’s sensations of touch and pain were mildly impaired in the four limbs. His position sense 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 (90%) and his forced expiratory volume in 1 second/forced vital capacity graph at inspiration and expiration showed poor movement of the diaphragm but no abnormality in the lung field. Routine haematological and serological studies gave normal results. No monoclonal or polyclonal proteins were detected. IgG and IgM antibodies to gangliosides GM1 and GD1b were negative. Analysis of CSF showed 1 lymphocyte/mm3 and 25 mg/dl protein. Motor nerve conduction studies showed prolonged distal latencies in the right median (8.8 m/s (normal value in our laboratory <4.6)) and ulnar (6.2 ms (normal <3.6)) nerves, and moderate decreased conduction velocities in the right median (50% (normal >45)), ulnar (45 m/s (normal >49)), tibial (35 m/s (normal >38)), and peroneal (29 m/s (normal >41)) nerves. There were moderate decreases in the amplitude of compound action potentials in all the nerves tested, and an amplitude reduction of 50% was detected across the cubital tunnel of the right ulnar nerve. Minimum F wave latencies were prolonged in all the nerves tested. The latency of the right phrenic nerve was slightly
mally thin axonal myelin sheaths. The density of the myelin sheath and some abnormalities were rare. A left sural nerve biopsy showed scattered tomaculous thickening of the myelin sheath and some abnormal 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 transient entrapment mononeuropathies, 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),¹ 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 hypventilation 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.¹

Diffuse proximal weakness in our patient is an uncommon finding as for HNPP. Mancardi et al.¹ 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.

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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 few 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 supraclavicular cord, 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. Electrodiagnostic studies were consistent with partial right accessory nerve 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 electrodiagnostic studies performed 1 year after CEA 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. Since then, there have been several case reports and small series.1 A 1996 review of reports of cranial neuropathy after CEA disclosed only one patient with spinal accessory neuropathy in over 3000 cases.1 Although the authors did not include several other reports2–4 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 CEA's that have been done worldwide suggests that clinically significant spinal accessory neuropathy is a rare complication. Many reports of 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.3 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 cataract dissection and retraction have been reported to precede spinal accessory neuropathy.1,4

The spinal accessory nerve courses along the internal jugular vein and near the internal carotid artery, typically well above the carotid bifurcation. This should suggest 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 unclear.

From our search, internal jugular venous thrombosis after CEA has been reported in only one case.5 As Southcott et al noted, retraction of the internal jugular during CEA may cause dissection, hematoma, and postoperative inflammation and scarring, leading to 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 as a result of neck dissection, often with recanalisation after several months.6

The presence of induration about the incision site and a palpable supraclavicular cord in our patient led us to suspect venous thrombosis. Symptoms of spinal accessory neuropathy or internal jugular venous thrombosis 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 and paraesthesia, fever and leukocytosis may occur.7

Common pathogenetic mechanisms for spinal accessory neuropathy and internal jugular venous thrombosis may include intraoperative traction, haematomata, 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 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 alert the sports 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 any 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 cerebral angiography were normal. Cerebral CSF examination showed no oligocytoplasia. D-dimers were within the normal range (360 ng/ml, normal <500 ng/ml). Creatinine was in the normal range (102 µmol/litre). Transesophageal echocardiography and ECG 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 200µg chromium per two capsules. The second drug contained 6000 mg creatine monohydrate, 1000 mg taurine, 100 mg inosine, and 5 mg coenzyme Q10 per scoop. He consumed 40–60 mg ephedra alkaloids, 400–600 mg caffeine, and 6000 mg 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 air flight, there was no deep venous thrombosis and D-dimers were normal. However, ephedrine has an indirect sympathomimetic action by releasing norepinephrine for arteriole vasoconstriction in addition to other catecholaminergic effects. Both ischaemic and haemorrhagic stroke associated with ephedrine use have been reported.1,2 Acute myocardial infarction and acute psychosis have also been reported after taking ephedrine and other sympathomimetic drugs.3 Ephedrine and its metabolites are natural products that are used in non-prescription medicines for multiple uses. Ephedrine is an ingredient in MaHuang extract, which contains ephedra alkaloids, in multitudes of energy supplements.1 It has been associated with increases in blood pressure, heart rate, and stroke volume. In addition, it increases metabolism and reduces appetite and increases dopamine levels. It has also been associated with a toxic psychosis. It is used in non-prescription medicine in most countries, and it is commonly used by American athletes and bodybuilders.1

In addition to sympathomimetic side effects, MaHuang extract and crystalline monohydrate have many cardiovascular side effects. It has been reported with the use of creatine monohydrate, this compound, used in association with other drugs as energy supplement may have deleterious side effects. This may be particularly true when used at high doses in combination with sympathomimetic drugs as in our patient. Renal dysfunction has also been reported after oral creatine supplements. Our patient had a slight increase in creatinine 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 effects of energy supplements, particularly when used in multiple combination.

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1 Petroclival meningioma as a cause of ipsilateral cervicofacial dyskinesias

Hyperkinetic movement disorders of facial and neck muscles such as blepharospasm, hemifacial spasm, 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 dysaesthesia 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. Oculo-vestibular response to caloric stimulation was

(A) Axial T2 weighted SE MR images of a 32 year old woman with left sided cervicofacial dyskinesias show a large left petroclival meningioma compressing the brainstem. (B) Coronal inversion recovery MR scans demonstrate marked displacement and distortion of the brainstem due to the petroclival meningioma. (C) Gadolinium enhanced axial T1 weighted SE MR scans 3 months postoperatively show complete removal of the tumour and normalisation of the displacement of the brain stem.
decreased on the left side. Furthermore, there was mild left dysdiadochokinesis. 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 cerebellomotor pontine region, extending to the contralateral side (figure A and B). Necropsy showed a discrete focus of ischaemic infarction in the brainstem, consistent with acute infarction of the motor cortex.

The postoperative improvement of the dyskinetic cervicofacial movement disorders. It is likely that the brainstem within the posterior fossa had changed. Postoperative imaging showed no new deficits. The facial palsy improved slightly as well as the trigeminal hyposthesia. Audiology 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 causative association between the pectori vesicular 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 patients with dystonic neurinomas, meningiomas, and epidermoid tumours of the cerebellopontine angle.2 Acoustic neurinomas and anaplastic pontocerebellar glioma can be associated with facial myokymia and spastic parietic 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 centered on 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. 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.5

Our case provides further evidence that functional impairment by compression and distortion of the brain stem may cause hyperkinetic cervicofacial movement disorders. It is supported also by the lack of movement disorders accessible to surgical treatment of the underlying pathology. Therefore, patients with cranial or cervical dystonia or choreic dyskinesias should undergo MR imaging to rule out a surgically treatable cause.

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Acute multifocal cerebral white matter lesions during transfer factor therapy

Transfer factor is a naturally occurring substance secreted by lymphocytes of known antigenic specificity. This molecule is known to transfer the antigen specific response in patients with the human T cell mediated antigen specific response. Transfer factor has been reported to stimulate the cell mediated immunity in an antigen specific fashion.1 The mechanisms of action of transfer factor are still far from clear; in vitro dialysable leucocyte extract increases macrophage activation and interleukin (IL) 1 production and enhances leucocyte chemotaxis and natural killer function. Transfer factor has been reported to stimulate the cell mediated antigen specific response in patients with various infections2; therefore, treatment with transfer factor has been suggested in patients with selective deficits in cell mediated immunity such as in some refractory neoplasms and chronic infections. Moreover, it has been used in the treatment of uveitis.3 Administration of dialysable leucocyte extract has seemed to be free of hypersensitivity, long lasting side effects, or complications, except for transitory hyperpyrexia.4

We report on a patient in whom multiple cerebral white matter lesions developed after taking dialysable leucocyte extract orally for a year. A 28 year old man was admitted to hospital because of headache, mental confusion, and right hemiparesis. He had had recurrent bilateral uveitis from the age of 12 to 14 with reflux in the right eye. In January 1995 retinal vasculitis was diagnosed at fundoscopy and in July 1995 he started oral transfer factor as dialysable leucocyte 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 right Babinski's sign. No fever or meningismus were present. 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 but 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 leucocyte 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 casual. 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 antinuclear antibodies is found in 2% of healthy subjects.

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. In addition, CSF without oligoclonal banding argues against a diagnosis of multiple sclerosis, whereas it is commonly found in acute disseminated encephalitis. On the other hand the possibility that acute disseminated encephalitis may recur has been accepted and on the basis of the patient's clinical picture and CSF, we favoured such a diagnosis.

The pathogenetic 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 autoreactive 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 IL-2 in patients with malignancies or HIV infections.

On the other hand, the fact that acute disseminated encephalitis is often correlated with the administration of foreign proteins, such as during vaccinations or viral infections 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 disease—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 Depoprovera 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 stood 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 in 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 impairment of fine finger movements, dysgraphaesthesia on sensory testing, and a manneristic gripping handshake. There were no extrapyramidal

Brain CT, axial section: dense calcific deposits in the basal ganglia, thalamus, and orbitofrontal cortex consistent with Fahr's disease.
symptoms. His IQ score was in the low range (WAIS-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), 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). Similar 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 0.70–1.34 mM); and parathyroid hormone was below 0.6 (normal 1.0–6.55 µM/l). Laboratory tests were normal, confirming the absence of rheumatoid arthritis, metabolic disease, or gout. Surgical removal via a transoral approach with a minimal bone 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 ligamentary tissue. In a task assessing the understanding of others’ intentions, these two clinical coincidences be instructive for a neurodevelopmental model of autism.

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

The craniovertebral junction can be affected by several pneumotumorous masses extracranial, which are of various aetiologies. Cognitive and behavioural abnormalities may be present when calcifications occur early in development. A fortuitous association between pervasive developmental disorders and hydrocalasia, given the paucity of published cases, is plausible in the presented patient. Nevertheless, our case suggests that abnormal phospho-calcium metabolism could produce an autistic syndrome when brain calcifications cause specific neuropsychological deficits, due to their localisation. For example, errors of social judgement may be related to calcifications of the orbitofrontal cortex, whereas dysfunction of frontal–basal ganglia circuits may contribute to repetitive and ritualistic activities. Additionally, developmental lesions of the basal ganglia and cerebellum may contribute to the abnormalities of sensory attention, procedural learning, and motor intention in this patient.

The finding that the clinical picture of autism can be found in a wide range of medical conditions giving rise to organic brain dysfunction is not new, but the relation between these conditions and autism are often considered meaningless. By contrast, this case, similarly to some others suggests that dysfunction in key brain circuits may result in behavioural and cognitive abnormalities currently indistinguishable from idiopathic pervasive developmental disorder. This case also suggests that careful biological assessment of this group of patients may disclose focal brain lesions associated with identifiable cognitive deficits. Could these clinical coincidences be instructive for a neurodevelopmental model of autism?

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

The craniovertebral junction can be affected by several pneumotumorous masses extracranial, such as rheumatoid panus, hypertrophic non-union of odontoid fracture, tophaceous gout, calcification of dura mater, or gout. Surgical removal, symptomatic patients responded patient. Nevertheless, our case suggests that abnormal phospho-calcium metabolism could produce an autistic syndrome when brain calcifications cause specific neuropsychological deficits, due to their localisation. For example, errors of social judgement may be related to calcifications of the orbitofrontal cortex, whereas dysfunction of frontal–basal ganglia circuits may contribute to repetitive and ritualistic activities. Additionally, developmental lesions of the basal ganglia and cerebellum may contribute to the abnormalities of sensory attention, procedural learning, and motor intention in this patient.

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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. On T1 weighted images taken 3 days later showed an intraparenchymal lesion, at the left ambient cistern without other intracranial lesions. On and linear high density at the left 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 level, 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 cranioocervical injury. Responsible lesions for sensory impairment, detectable by neuroimaging studies, almost always accompany associated neurological deficits. To our knowledge, a selective injury at the spinalthalamic 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 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.

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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. Thus, 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 al and comment on the medical treatment of toluene induced tremor. Microdialysis experiments in rats have shown that inhalation of toluene increases extracellular γ-aminobutyric 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. Degeneration of certain cerebellar pathways is probably responsible for the loss of this dopaminergic innervation. Dopamine agonists could therefore be of potential interest in the treatment of toluene induced tremor. This hypothesis was explored in a recently described case, which showed remarkable clinical and iconographic similarities with that described by Miyagi et al: (a) long history of chronic toluene inhalation, (b) marked postural tremor, (c) progressive worsening of the symptoms despite absence from inhalant misuse, and (d) mild cerebral atrophy and marked low signal intensity in globus pallidi, thalami, red nuclei, and substantia nigra on T2 weighted MRI. As our patient’s tremor was progressive, medical treatment with a dopamine agonist was considered. One particular agent (amantadine) caught our attention because it had proved successful in the treatment of postural tremor of heredodegenerative disorders in which the dentatorubro-olivary system is affected. In addition, there is evidence that catecholaminergic pathways are also involved in this type of ataxias, supported by loss of one of these neurotransmitters in the CSF of patients with heredodegenerative ataxias. In our patient, amantadine hydrochloride (100 mg twice daily) abolished postural tremor and ataxia completely over a 3 month period.

Subsequently, the treatment was discontinued, which resulted in relapse of the tremor and ataxia. He was rechallenged to amantadine hydrochloride (100 mg twice daily) and ataxia. He was rechallenged to amantadine hydrochloride (100 mg twice daily) abolished postural tremor in the CSF of patients with heredodegenerative ataxia. We hence reported our experience.

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

Nabbout et al have attempted to identify the risk factors for the progression of subependymal nodules into giant cell astrocytomas (SEGAs) in 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 the risk factors identified by Nabbout et al 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 hence the positive predictive value of any screening test in a general population of patients with tuberous sclerosis complex is understood well.

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The second point 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 Monro. It is not certain that all SEGAs arise from lesions close to the foramen. They may arise in the fourth ventricle. Furthermore, the later presentation of many lesions in the lateral ventricles has, in the past, precluded accurate determination of their point of origin. 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 Monro”. Inclusion of such cases is given 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 what 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. However, the point of this study was that the authors have attempted to identify the risk factors for the progression of subependymal nodules into giant cell astrocytomas (SEGAs) in 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.

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 al 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 al coined the term flail 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, Kata et al 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 diplegia syndrome. Other terms used in the past to refer to this form of ALS have been dangling arm syndrome, suspended form, 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 scapulohumeral form, or the chronic anterior polyneuropathy reported by Vulpiani in 1886 and known in Franco-German literature as Vulpiani-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 scapulohumeral distribution (over 45 years of age) generally leads to ALS as a matter of course. 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 longer median survival (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 ambulatory ability, albeit with gait disorders, for more than 5 years after the onset of symptoms.

From a personal viewpoint, we also note two findings characteristic of these patients. In the initial stages of the illness, there is a notable difference between 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 (FVC, 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 deltoideus (and the pectoralis minor) and a loss of strength in the external rotation of the shoulder (infraespinaus, supraespinaus, and teres minor). As a consequence, the upper limbs adopt an atypical position, with the shoulders slumped, and the arms, forearms, and hands in pronation.

The atrophy and weakness of the infraespinaus and the supraespinaus, 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 atrophy 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 85. 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 Gamez et al for their interest in our article concerning the atypical form of amyotrophic lateral sclerosis (ALS).

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 arm girdle and the 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 Gamez et al cite, many terms have been coined to describe this peculiar pattern of the muscular atrophy such as flaring arm, orang utan sign, dead arm sign, suspect flail arm syndrome, amyotrophic brachial diplegia syndrome, biciphalic palsy and man-in-the-barrel syndrome. Some researchers classified it into a category of motor neuron disease (ALS or spinal progressive muscular atrophy). However, others could not exclude the possible cause of cervical diseases such as dissociated motor loss in the upper extremity.1 In fact, these patients had cervical abnormalities such as cervical spondylosis and foraminal stenosis.2 It is possible that this patient had chronic irritation of posterior longitudinal ligament disclosed by cervical radiography, MRI, or myelography. By contrast with clinical awareness of this peculiar pattern of muscular atrophy, no pathological correlation has been made until we first reported necropsy cases in our articles.3 Now, these patients with their peculiar pattern of muscular atrophy are considered to be ALS or a subtype of ALS. In my private opinion, “dangling arm syndrome” or “dead arm sign” seems to be the most suitable term depicting this type of motor neuron disease.

I agree with Hu et al reporting four important statistical discoveries in this form of ALS: the prevalence percentage of 10% of the whole ALS group, the similar age onset to the rest of ALS, a predominance among men (the male/female ratio was 1:1 in this study), and a longer median survival. It is clinically important to give wider publicity to the existence of this atypical form of ALS to avoid unnecessary surgical intervention for cervical abnormalities.

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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.1 As in their patients transcranial magnetic stimulation induced absent or delayed corticoluminal responses at the tongue, the authors ascribed isolated dysarthria to interruption of the corticolimbic pathways. On the whole, the article is 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.2 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-pharyngeo-glosso-mandibular apraxia (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 the language areas, resulting in dysfunction of these cortices.3 Therefore, we postulated that isolated dysarthria results from interruption of cortico-subcortical networks indispensable for speech output, involving the thalamocortical and cortico-striatal 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.

To assess cortico-ponto-cerebellar tract function, Urban et al investigated cerebellar blood flow in patients with isolated dysarthria using HMPAO-SPECT. The authors reported that the cortico-ponto-cerebellar tract was 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.4 Linguinal palpation evidence 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 cortico-subcortical diaschisis. 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.
The discrepancy between the two studies may not be mainly due to the different stage of the disease between the two groups of patients. Although the duration of the disease is one factor to judge the disease stage, the severity of the disease (stage of the disease) is also positively correlated with CAG repeat length. 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, however, at least, that the pathological 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 have no difficulty in showing normal inhibition, but have much difficulty in showing reduced or absent inhibition because of such marked dependence of the results on the intensities of magnetic stimulation. Therefore, we used 100% of the resting threshold as a conditioning stimulus before we confirmed inhibition in studies of patients. We used an intensity of 5% less than the active threshold as a conditioning stimulus in our magnetic stimulation study. This may induce a difference of sensitivity of the test, and the amount of intracortical inhibition in our normal controls is greater (see also) than in the study of Hanajima et al.

When interpreting the results of studies with paired transcranial magnetic stimulation pathophysiologically it should be kept in mind that similar changes of intracortical inhibition have been shown in patients with various movement disorders (focal dystonia, myoclonus, parkinsonism, restless legs syndrome, Tourette's disorder), but also in different diseases such as amyotrophic lateral sclerosis. We think, therefore, that the impairment of intracortical inhibition cannot be regarded as the marker of a specific pathophysiological mechanism, but is likely to reflect a non-specific imbalance of inhibitory and facilitatory circuits within the motor cortex.

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Motor cortical excitability in Huntington's disease

We read with great interest the paper of Hanajima et al. reporting that intracortical inhibition of the motor cortex is normal in patients with chorea of various origins. At variance with the results we previously found a reduced intracortical inhibition in a group of patients with genetically confirmed Huntington's disease. Hanajima et al suggest that the discrepancies between the two studies may be due to infarction in other parts of the brain compared with the lesion causing pure dystarhria. P URBAN
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The authors reply:

We were very grateful for the response of Abbruzzese et al to our paper. We completely agree with their opinions.
intracortical inhibition is often decreased even in normal subjects. The 50% 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 decreased in Huntington’s disease. This slight abnormality could be detected with their method but not with ours because their method has better sensitivity in detecting an abnormality than ours. Whether its 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. They show 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 the definition of CCP. The CCP of about half of CVR0 is equal to CCP (5).

Secondly, 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 will not collapse (ABP=CCP), it is not possible to decide whether their actual wall tension is determined more by transmural pressure or by active vasoconstriction. 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 = 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:

\[ \text{FV} = (\text{ABP} - \text{ICP})/\text{CVR0} \]

(6) and equation 5 to:

\[ \text{CPP2} = \text{ABP} - \text{ICP} = \text{CPP}1/\text{CVR0} \]

(7)

Equation 7 explains well the positive correlations found between CCP2 and ABP and between CCP2 and ICP, respectively, without assuming a connection between CCP2 and Burton’s concept of “critical closing pressure”. The second criticism was that our CCP concept of the authors.

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Czosnyka et al. reply

We thank Diehl very much for the interesting letter providing some mathematical considerations about cerebral haemodynamics. We need to emphasise that our primary intention 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:

\[ \text{CCP} = \text{ABP} - \text{ABPpp} + \text{FVpp} \]

(where ABP and FV are mean values of arterial pressure and MCA flow velocity, ABPpp and FVpp are systolic values, ABPpp and FVpp are peak to peak amplitudes). A graphical interpretation of this formula is given in fig 1. CCP is a point of linear regression between subsequent systolic and diastolic values recorded within 6 seconds 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:

\[ \text{CCP} = \text{ABP} - \text{A1}/\text{FV} \]

In our paper we confirmed empirically that both CCP1 and CCP2 produced the same values in a group of patients after head injury, therefore the mathematical consideration of Diehl (equations 1–5) must 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 (equation (1) implies). Therefore “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. Therefore, 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. In our material equivalent of parameter CVR0 (as defined by Diehl) is 1.007 (SD 0.31) and CVR1 0.972 (SD 0.32); the difference however is not statistically significant. Therefore, the suggestion that the CVR1/CCR0 ratio is 0.5 is not correct. Real CVR0 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 we have never suggested anyone could do so.”

The second criticism was that our CCP concept was positively correlated with ICP. It is not a surprise. When ABP decreases, vasodilation occurs and arterial wall tension decreases. Therefore presetting ICP was constant, CCP should decrease. A rather weak (though significant) correlation suggests that not all of our patients were 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
High frequency stimulation of the subthalamic nucleus and levodopa induced dyskinesias in Parkinson's disease

Reduction in the neuronal activity of the subthalamic nucleus leading to diminished excitation of the globus pallidum internum is associated with chorea-ballism in monkeys. Levodopa induced dyskinesias are currently thought to share a similar pathophysiology. 

Levodopa induced dyskinesias are currently associated with chorea-ballism in monkeys. The role of the globus pallidum internum is induced dyskinesias in Parkinson's disease.

High frequency stimulation of the subthalamic nucleus has been associated with the production of dyskinesias only relieved by reduction in levodopa intake. Moreover, Benabid et al who pioneered this technique, consider the induction of dyskinesias by high frequency stimulation of the subthalamic nucleus as a good indicator of a very positive response to surgery. 

The trajectory and length of the electrodes, which is blocked by high frequency stimulation. (3) When the recording electrode is removed, the activity was tonically firing neurons, and absent sensorimotor responses (“driving”). All these characteristics seemed 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 differentiation may not be easy. 

It is very important to document in more detail the findings in the case of Figueiras-Mendez et al. Ideally, we would like to see the trajectory and length of the different recording tracks, the effects of microstimulation, and the post-surgery MRI with measurements near the tip of the electrodes. If, as assumed, the subthalamic nucleus was indeed correctly targeted in this patient, the pathophysiology of the basal ganglia will need to be revisited.

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Figueras-Mendez et al reply

We thank Obeso et al for their comments regarding our recent report. In summary, they raised some interesting points which need further clarification.

Recognition of the electrical activity of the subthalamic nucleus was based on the following criteria: (a) high frequency discharge (25 Hz or higher) within the nucleus; (b) a tonic (regular), phasic (irregular) or a rhythmic pattern of discharge; (c) response to voluntary/purposeful movements; (d) When rhythmic discharges were recorded irregular passive manipulations were performed or the patients asked to move the limbs irregularly; (d) response to tremor activity. Positive cells were so considered based on the correlation with the EMG and the accelerometer recorded simultaneously. Artificial manual stopping by one experimenter (confirmed by visual inspection, silence in the EMG, and stoppage in the oscillating accelerometer) and/or spontaneous arrest in the tremor modified the firing frequency and discharge pattern or rhythmic cells corroborating the tremor nature of the cells; (e) the activity of the cells above the subthalamic nucleus. A lower background noise level; (f) the activity of substantia nigra pars reticulata cells when further lowering the microelectrode. These cells discharge at high frequency at regular intervals as identified in patients' and primates. All these points were fulfilled by the patient reported.

Considering the questions in the letter by Obeso et al, we make the following comments: (a) Action potentials of high frequency discharges are easily recognised from the rest of the recording cells, and are not very common. The recordings shown in the article have amplitudes less than 0.3 mV and could not be considered large amplitude potentials. We start to record activity from 3 mm before entering the subthalamic nucleus, traverse the length of the subthalamic nucleus, and go further down several mm to encounter substantia nigra pars reticulata cells. Changes in the background activity are clearly recognised and are higher when entering the subthalamic nucleus. Enough cells are recorded along the tracks experimented so as to recognize a large amplitude potential. The discharge pattern was that described in the literature. A recent anatomical study also showed that the cortical-subthalamic nucleus con- section 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 terminate in the lateral region of the subthalamic nucleus. All this heterogeneity may have pathophysiological relevance, describing properties of the cerebrovascular bed. Whether it simplifies our knowledge—we personally find it doubtful. Finally, we are truly obliged to Dierh for an opportunity to have this interesting discussion.
low background activity found in our recordings is only due to the better signal-to-noise ratio of the electrodes used. “Good recording electrodes” depend on many variables such as tip size, tip profile, insulation material, impedance, manufacture, etc." The signal-to-noise ratio of the cells in question has the same ratio as the subthalamic nucleus cell shown by Hutchinson et al.2

(b) In our report, cells discharged tonically, but also other cells fired phasically, well differentiated by a profuse burst activity and identified by statistical means (autocorrelation and interval histograms).

(c) Motor responses and tremorgenic cells in line with the above mentioned criteria were found along the trajectory of the electrode. Unfortunately, this point was not mentioned in the paper. It would surely have changed the opinion of Obeso et al.

In the mentioned patient, a total of eight neurons were recognised as belonging to the subthalamic nucleus in the right hemisphere, with a mean frequency of 74 Hz (range 38–109 Hz). Four of them responded to passive and/or voluntary movements, and one was considered tremorgenic. The stimulating electrode was placed in laterality 11. One track was performed. In the left hemisphere, two tracks were performed. One track was inhibited by the poor responding activity of the cells recorded. In the other track, nine neurons were recorded in the subthalamic nucleus (always following the above mentioned criteria) with a mean of 69 Hz (range 17–98 Hz). Five cells responded to passive and/or voluntary movements. One of them was also positive to tremor. The stimulating electrode was placed in laterality 12. The track performed stimulating electrode is always tested in the surgery before cementing it and, only when the symptoms are considered of unquestionable benefit it is left in the chosen place. The final position of the electrodes, ascertained by ventriculography, was as follows: (a) posterior/anterior: 1.5 mm behind the mean point of intercommissural line, (b) height: 6.5–6.5 mm below the intercommissural line, and (c) lateral: 12 mm for the right hemisphere, and 11.5 mm for the left hemisphere.

NITRIC OXIDE IN ACUTE ISCHEMIC STROKE

The pivotal role of nitric oxide (NO) in cerebral ischaemia has been elegantly highlighted in the recent editorial by O’Mahoney and Kendall.1 Although studies of neuroprotective agents have been largely disappointing, pharmacological manipulation of NO may represent a novel means of protecting the brain from ischaemic 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 ischaemia. Preliminary studies have shown that statins modulate brain nitric oxide synthase (NOS) activity in a neuroprotective manner. Data from a murine model of ischaemic stroke demonstrate that prophylactic statin therapy reduces infarct size by about 30%, and improves neurological outcome in normocholesterolaemic animals.2 In this investigation, statin therapy directly upregulated endothelial NOS in the brain without altering expression of neuronal NOS. Recent findings also suggest that statin therapy influences the activity of inducible NOS. Lovastatin has been shown to inhibit cytokine-mediated upregulation of inducible NOS and production of NO in rat astrocytes and macrophages,3 and this inhibition may represent a novel means of reducing pro-inflammatory responses that accompany ischaemia. Most interestingly, these preliminary findings suggest that statin therapy may modify the friendly and unfriendly faces of brain NO in a surprisingly neuroprotective manner. These and other vascular effects of statins in cerebral ischaemia are potentially of great importance in human neuroprotection and ongoing studies such as the The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study4 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 upregulates the activity of nitric oxide synthase (NOS) without affecting neuronal NOS. Their contention is that statin therapy may be neuroprotective. Statins may in fact 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 NOS as stroke preventive therapy. Rather, it is focused on the possible ways of inhibiting neuronal NOS and inducible NOS mediated nitric oxide release after the event of acute stroke. At present, there is no convincing evidence indicating that acute administration of statins in animal models of ischaemic stroke is neuroprotective. Their point about statins and endothelial NOS 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 it detracts attention from the act of narrating which detracts from realistic illusion, so reducing the emotional intensity of what is being represented. It is a device much favoured by postmodern writers, who expose the metafictional constructs. The intrusive medical author never dropped out of fashion, although in these days of evidence based prejudice, authorial omniscience 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 aetiology, cell injury, and repair. Next, a chapter on inflammatory demyelinating diseases examines 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 para-neoplastic disorders of the CNS, stiff man syndrome, neurological complications of...
connective tissue disorders, organ specific autoimmunity, 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 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


As Alzheimer's disease becomes of increasing importance to society, basic science research in this field needs to provide the building blocks for both 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 this 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 research from the correct diagnosis to basic science approaches of treatment is ambitious for such a compact book (315 pages), and although the editors succeed in collecting an interesting series of papers around these themes, they make no claims to be comprehensive in their scope. The papers included range from original research reports to reviews of the current literature. The review papers are generally excellent, concise, clear, well referenced, and illustrated—for example, there are excellent reviews of Alzheimer's disease with vascular pathology (Pasquier et al), and Lewy body disease (McKeith et al), great updates on neuropathology (Jellinger and Bancher, Braak et al), and several worthy reviews of treatment strategies for Alzheimer's disease including NSAIDS (Möller), antioxidants, and radical scavengers (Rosler et al). I found the review by Reisberg et al on ontogenic models in the understanding of the management of Alzheimer's disease particularly interesting. However, the papers of original research are of more limited interest to the general reader. Although, as mentioned, the quality of illustrations is good, there is some variability in the definition of abbreviations and occasional lapses into other European languages.

Certainly, I think this book would be of value for investigators interested in the neuropathology, immunopathology, and molecular biology of Alzheimer's disease. It would make an excellent addition to libraries as a reference text for many researchers of varied interests.

CLARE GALTON


Organ transplantation, once medical exotica, is now almost routine. In the United Kingdom each year are performed cadaveric organ transplants of about 1800 kidneys (in addition to 160 live kidney donors), 700 livers, and 450 heart/lungs (UK Transplant Support Service). If not basic surgical techniques were established at the beginning of the century in canine models. Translating these experiments to humans awaited safe and effective immunosuppressive agents. Until recently, the two forms of immunosuppression were radiation (total body or total lymphoid) and non-selective chemical reagents (benzene and toluene).

Then the antiproliferative drug 6-mercaptopurine (6-MP) was introduced, shortly followed by a derivative, azathioprine, with improved oral bioavailability. Combined with corticosteroids, these allowed the first human solid organ transplants to be performed: in 1954, the first lung transplant in Mississippi and liver transplant in Colorado. Then in 1967 Christian Barnard captured the world's imagination with the first heart transplant. His technique has been modified slightly since, but the increasing success of organ transplantation rests mainly on improved immunosuppression with drugs that selectively suppress lymphocytes by inhibiting lymphokine generation (cyclosporin A, tacrolimus), renal transplant (sirolimus, leflunomide), or differentiation (15-deoxyspergualin) pathways. As a result, over the last 10 years in the United Kingdom, the 1 year survival of grafts has improved from 80% to 90% (kidney), 55% to 75% (liver), and 70% to 90% (heart/lung).

Wijdicks estimates that 10% of transplant patients have a significant neurological complication. But the commonest being neurotoxicity of immunosuppressive drugs, seizures, and failure to awaken. Yet this is the first text devoted to the neurological aspects of organ transplantation. It is therefore a timely subject, particularly the increasing use of sirolimus and tacrolimus.

Butch (Wijdicks) estimates that 10% of transplant patients have a significant neurological complication. But the commonest being neurotoxicity of immunosuppressive drugs, seizures, and failure to awaken. Yet this is the first text devoted to the neurological aspects of organ transplantation. It is therefore a timely subject, particularly the increasing use of sirolimus and tacrolimus.

Certainly, I think this book would be of value for investigators interested in the neuropathology, immunopathology, and molecular biology of Alzheimer's disease. It would make an excellent addition to libraries as a reference text for many researchers of varied interests.

CLARE GALTON

ALASDAIR COLES


Volume nine of the Current Issues in Neurodegenerative Disease series examines the interplay between cerebrovascular disease and dementia, particularly Alzheimer's disease. Two hundred pages of what are essentially 20 brief review articles comprise this text, sadly without any illustrations. Furthermore, there is no introduction to each chapter there is a certain sense of deja vu, although on the positive side each contribution is extremely well referenced.

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 contributions that 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 in 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 unproved angiopathy and recurrent lober 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 further 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


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 by interweaving 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 older 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 disclaimers seem 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 relevance to neurologists, obstetricians, general practitioners, midwives, and trainees.

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 availability of evidence to support the statement “no monotherapy human abnormally reported” with certain new antiepileptic drugs in pregnancy, (d) the need to consider the impact of the drug on the patient and the patient’s family, and (e) the results of clinical trials or formal research. This disclaimer 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 relevance to neurologists, obstetricians, general practitioners, midwives, and trainees.

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.

LINDA NASHEF
Ischaemic stroke in a sportsman who consumed MaHuang extract and creatine monohydrate for body building
K VAHEDI, V DOMIGO, P AMARENCO and M-G BOUSSER

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http://jnnp.bmj.com/content/68/1/112

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