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 Antiepileptic drugs were withdrawn to facilitate seizure recording.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 generalized tonic-clonic seizure after video-EEG telemetry, she began to develop emotional lability, talking nonsense, motor restlessness, and auditory hallucination. A cerebral SPECT study was performed at day 4 after her last seizure. Her psychotic features persisted although she was taking antipsychotic medication (pimozide). Cerebral SPECT showed a clear hyperperfusion signal over the right lateral temporal neocortex and contralateral basal ganglion. An interictal cerebral SPECT study was repeated at 4 weeks after postictal psychosis which showed a complete resolution of hyperperfusion signal in the right temporal lobe and basal ganglia. Anterior temporal lobectomy was performed and she became seizure free after surgery.

Patient 2 was a 44 year old man with intractable complex partial seizures since the age of 30. His seizures were intractable to multiple antiepileptic drugs. Brain MRI showed left hippocampal sclerosis. Interictal cerebral SPECT showed a relative hyperperfusion 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. A 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...

Interictal SPECT and SPECT performed during postictal psychosis. (Top) A SPECT study of patient 1 showing areas of relative hyperperfusion over the right temporal neocortex (red arrows) and the left basal ganglia (blue and yellow arrows) during postictal psychosis. (Bottom) SPECT study of patient 2 showing areas of hyperperfusion over the right temporal neocortex and the left basal ganglia. Arrows indicate areas of hyperperfusion.
started after the cerebral SPECT. His psychotic symptoms resolved 2 weeks later with full recovery.

Cerebral SPECT performed during the interictal period (IP) and during postictal psychosis (PP) were analysed visually and areas of hypoperfusion were identified. Quantitative data at regions of interest (ROIs) were measured on coronal and axial slices containing basal ganglia (BG), mesial (MT), and lateral (LT) temporal lobe structures. Symmetry 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 in comparison with their interictal study (figure). Quantitative analysis for patient 1 showed changes of ASI during IP and PP over right MT was +75% (+6.4647 to −1.6528); over the right LT was +116.7% (1.07927 to 12.55764); and over the left BG was +206.8% (+0.73733 to 2.21574). Quantitative analysis for patient 2 showed changes of ASI during IP and PP over right MT was −8% (13.14217 to 12.64158); over right LT was +178.6% (10.4696 to 18.70057); and over left BG was +155.9% (+5.85556 to 3.27522).

Postictal psychosis is a distinct clinical event associated with temporal lobe epilepsy.1 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 postictal psychosis is usually benign. Antipsychotic drugs,1–3 good prognosis. Antipsychotic drugs, such as haloperidol and fluphenazine are usually prescribed.1

The underlying mechanism of postictal psychosis is unknown. Postictal cerebral hypofunction has been postulated as an analogue to Todd’s paralysis after seizure.1–2 However, the presence of increased rCBF during postictal psychosis may suggest an alternative explanation as ictal SPECT has during postictal psychosis, may suggest an alternative explanation as ictal SPECT has been performed on 5 µm thick cryostat sections using a protocol reported previously.1 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 by phage 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).

Control sections were processed identically to the other specimens, but the primary antibody was substituted with a specific immunoglobulin of recombinant antibodies. The antibodies were blocked using the specific antigens. The antibodies were recombinant proteins containing the epitope produced in E Coli. For the mAb BC-1 we used the recombinant protein containing the type-III repeats 7B–8. For the mAb IST-4 we used the recombinant protein containing the type-III repeats 2–8. For the recombinant antibodies TN-11 and TN-12 the recombinant type-III repeat C and the recombinant fragment containing the EGF-like repeats were used.

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 located 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 with the TN-11 Ab fragment showed occurrence of type III repeat C TN isoform in the inner layers of the vascular components of the nidus, irrespective of their morphology. Six out of the 10 examined specimens were found to contain portions of cerebral tissue surrounding the angiomatous nidus. In all these 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.

### Characterisation of the employed Abs and distribution of the recognized isoforms.

<table>
<thead>
<tr>
<th>Anti-FN mAbs</th>
<th>Anti-TN Ab fragments</th>
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<tr>
<td>IST-4</td>
<td>TN-12</td>
</tr>
<tr>
<td>IST-9</td>
<td>TN-11</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Recognised isoforms</th>
<th>Total FN</th>
<th>Isolofs containing the ED-A sequence</th>
<th>Total TN</th>
<th>Type III repeat C Isoform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution of the isoform (n)</td>
<td>Widespread</td>
<td>Widespread</td>
<td>Widespread</td>
<td>Widespread</td>
</tr>
<tr>
<td>Isform containing the ED-B sequence</td>
<td>Absent in adult tissues (with the exception of the regenerating endodermum)</td>
<td>Present in the vascular wall and the matrix of fetal tissues and tumours</td>
<td>Absent in adult tissues</td>
<td>Present in fetal tissues</td>
</tr>
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</table>

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

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

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

Furthermore, use of the cell proliferation marker MB1 showed endothelial proliferation in arterioles, venules, and capillaries of the cerebral tissue neighbouring AVMs.

The present findings indicate that a particular FN isoform, mainly expressed by the vasculature of fetal and tumorous tissues, as well as a TN isoform typically detected in the walls of vessels in anaplastic gliomas, also occur in AVMs and in vessels of adjacent cerebral tissue, but that both isoforms are absent in normal brain. This evidence provides further support to the hypothesis of ongoing angiogenesis in and around these lesions.

The presence of angiogenic features in AVMs might result from maintenance of proliferating and remodelling potentials, or from a specific response to haemodynamic stress in vascular structures subjected to increased blood flow and pressure. Occurrence of these features also in vessels lying in areas peripheral to the nidus might be related to recruitment of the neighbouring vasculature, possibly dependent on focal ischaemia in the setting of arteriovenous shunting. However, the presence in apparently normal vasculature of molecules typically occurring in fetal tissues and malignancies indicates that cerebral AVMs may not be static lesions. Further studies are needed to ascertain whether this phenomenon results merely from haemodynamic stress or actually reflects an intrinsic growth potential. Should this second be the case, current therapeutic strategies would possibly require revision.

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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 thyroid failure in this country, it is likely that these have been present in at least some of Asher's original 14 cases. Although most had florid myxoedematous features at psychiatric presentation, this may simply reflect the delayed onset 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 hallucinatory, uncharacteristic behaviour. He had reported a vision of the crucifixion, and hearing the voice of his dead mother. He claimed that his health was only supported 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...
became aggressive and threatened them with a saw. The general practitioner was called and suspected "shock" as a new psychosis, and a severe depressive illness. Police assistance was requested because of the patient's continuing violent behaviour.

On admission he was untroubled but cooperative and appeared well. 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 his mild naming deficit, and poor performance on the Rey figure, which was due to planning rather than visuospatial disturbances, despite the presence of increased antimicrosomal antibodies. Anamnesis showed widespread mild cortical hypoperfusion. Thalidomide (2 mg twice daily) was started on admission he consistently rationalised all psychiatric symptoms and appeared well. There was no insight into the abnormal mental state. The psychiatric component of his illness resolved fully, and the antithyroid microsomal antibody titre fell markedly after thyrin replacement, although his mild neuropsychological deficits remained unchanged. Corticosteroids were not used at any stage.

The response to thyroxin does not, in itself, imply that the cerebral illness had an endocrine origin; a recent report described a patient with a subacute encephalopathic illness and compensated hypothyroidism in the presence of increased antimicrosomal antibodies, all of which responded to thyroxin replacement alone.4 In that case, however, both EEG and SPECT were abnormal, the SPECT showing multiple areas of severely reduced perfusion, which normalised with treatment. By contrast, in the present case the EEG was normal and the SPECT abnormality was marginal and changed little, if at all, with treatment. The evidence for a significant vasculitic component to the illness is, therefore, unconvincing.

The mild and relatively circumscribed neuropsychological deficits coupled with florid psychotic phenomena, also contrast with the profound global disturbance of cognition usually associated with Hashimoto’s encephalopathy.4 This distinction suggests that microvascular dysfunction and thyroid hormone depletions may explain different aspects of the clinical range in Hashimoto’s encephalopathy. Although the present case would support Asher’s conclusion that the psychiatric features of Hashimoto’s encephalopathy typically respond to thyroid replacement, it additionally suggests that subtle neuropsychological deficits may be apparent even in the absence of obvious cerebral perfusion deficits, and that these may not be fully reversible.

### Table 1 Laboratory and neuropsychological results at presentation (A) and at 12 month follow up (B)

<table>
<thead>
<tr>
<th>Laboratory (units)</th>
<th>A</th>
<th>B</th>
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<tbody>
<tr>
<td>Full blood count</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Erythrocyte sediment rate</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Urea and electrolytes</td>
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<td>Normal</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Anticoagulant level</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>B12 and folate</td>
<td>Normal</td>
<td>Not tested</td>
</tr>
<tr>
<td>VDRL</td>
<td>Normal</td>
<td>Not tested</td>
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<tr>
<td>Thyroid stimulating hormone (mU/l)</td>
<td>56.4</td>
<td>0.89</td>
</tr>
<tr>
<td>Free T4 (pmol/l)</td>
<td>Not tested</td>
<td>Not tested</td>
</tr>
<tr>
<td>Antithyroid microsomal antibodies titer</td>
<td>1:25600</td>
<td>1:1600</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Liver function tests</td>
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<td>Normal</td>
</tr>
<tr>
<td>Full blood count</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Thrombin resistance</td>
<td>25/30</td>
<td>25</td>
</tr>
<tr>
<td>NART IQ</td>
<td>10 16th percentile</td>
<td>16th percentile</td>
</tr>
<tr>
<td>WAIS-R (verbal)</td>
<td>138 percentile</td>
<td>Not tested</td>
</tr>
<tr>
<td>WAIS-R (performance)</td>
<td>27th percentile</td>
<td>Not tested</td>
</tr>
<tr>
<td>FAS verbal fluency (&gt;30)</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Cognitive estimate test (&lt;60)</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Graded naming test (&gt;15)</td>
<td>10/30</td>
<td>16/30</td>
</tr>
<tr>
<td>Digit span forwards (&gt;5)</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Rey-Osterreith complex figure (copy) (36)</td>
<td>25.5</td>
<td>24</td>
</tr>
<tr>
<td>Rey-Osterreith complex figure (recall) (30%)</td>
<td>Not tested</td>
<td>75%</td>
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</table>

### References

### Alien hand sign in Creutzfeldt-Jakob disease

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

Creutzfeldt-Jakob disease, one of the human prion diseases, is characterised by rapidly progressive mental and motor deterioration.1 Voluntary movements occur in above 90% of the patients in the course of the disease, the most common being myoclonus.2 Other movement disorders range from tremor to chorea, athetosis, dystonia. 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”.3 One of the patient’s hands acts as a stranger to the body and is uncooperative. Thus, there is 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,4 infarction of the medial frontal cortex, occipitotemporal lobe, and alcohol abuse,5 and corticobasal degeneration.6–7 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 before his 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 a sense of being watched, and an attendant fear that the “ceiling was nacreous and the whole place was alive”.

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 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 convulsive, haemorrhagic, or disturbed by hallucinations. The affect was sad and he had partial insight for his mental dysfunction. He was disoriented for time, place, and situation. He could understand speech and was able to follow instructions 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, haematology, and sedimentation rate was normal. The patient had no cortical sensory loss. Brain CT showed mild 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 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 few weeks later. Postmortem examination was not allowed.

This short fatal neurological disease manifested by fulminant dementia, myoclonic jerks, and extrapyramidal and cerebellar dysfunction 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 appeared 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...wanndered out of her view". In the second, the alien limb performed complex actions such as unbundling 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 or 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 non-callosal form, there is grasping and utilisation behaviour of the dominant hand. In the corticobasal degeneration, there are aimless movements of either hand. When a consequence of a tumour 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 corticobasal degeneration. The authors described the alien limb as “involuntarily rising and touching the mouth and eyes” (patient 1). The patient thought that she “was powerless to stop this movement” and when directed to stop responded that “she didn’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, corticobasal degeneration, and progressive multifocal leukoencephalopathy, in which an alien hand sign has also been described, is multifocality. In corticobasal degeneration, it was proposed that more than one site is affected or that a “release” phenomenon occurs accounting for the aetiology of alien hand. In CJD, bilateral cortical damage to motor areas might be the origin of their subsequent isolation and disconnection.

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

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

Recurrent peripheral neuropathy in a girl with celiac disease

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

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

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

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

Laboratory investigations showed a white cell count of 9300/mm³. The results of the following investigations were within the normal limits: haemogram, erythrocyte sedi-mentation rate, serum uric acid, urea, creatinine, glucose, transaminase, bilirubin, immunoglobulins (Igs), lead, iron, copper, urinalysis, urinary porphyrin, folate acid, and vitamins A, B₁, B₆, B₁₂, and E. Antibodies to Campylobacter jejuni and to Mycoplasma pneumoniae were negative. Antiviral antibodies, specific and non-specific organ autoantibodies, IgA and IgG antiglia- din antibodies (AGAs), IgA antiendomysium antibodies (EmAs), and IgA antireticuluit antibodies (ARA), as assessed by enzyme linked immunosorbent assay (ELISA) and immunofluorescence (IF) were also negative. Lumbar puncture was not performed. Antibodies against gangliosides GM₁ and GQ₁b, myelin associated glycoprotein and myelin
basic protein were not tested. Nerve conduc-
tion studies were consistent with a predomi-
nately motor demyelinating peripheral neu-
ropathy (table). Her symptoms improved spontane-
ously and she was discharged home after 2 weeks. For 2 years she was asympto-
matic on a gluten free diet.

At the age of 12 she presented acutely with severe abdominal pain 8 days after a weekly intake of bread meant to be gluten free. Two weeks later, due to persisting gastrointestinal symptoms, her parents excluded the bread from her diet. After 2 further weeks, while the abdominal pain was gradually improving, she had a new episode of acute weakness in the lower limbs and sensory abnormalities including burning paraesthesiae. On neurologi-
cal examination the legs showed marked decrease in muscle power; absent deep tendon reflexes, and a reduction in pain and temperature; light touch, perception of posi-
tion, and vibration were preserved. Walking was impaired and the patient was bedridden. Otherwise the examination was normal.

A haemogram showed white cell counts of 9700/mm³. Laboratory investigations were within normal values as in the past. IgA and IgG AGA, IgA EMA, and IgA ARA as assayed by ELISA and IF were again negative. Nerve conduc-
tion studies confirmed the presence of a predominantly motor demyelinating neu-
ropathy (table). The parents refused consent for a lumbar puncture or nerve biopsy.

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

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

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

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

The present case, however, differs clinically from those with neurological involvement previ-
ously 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 neuro-
physiology was strongly suggestive 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 associa-
tion with strong evidence of a genetic susceptability 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.2 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 in the course of the course of the disease or after follow up.

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

In conclusion this case shows two major issues: an acute polyneuropathy can be a complication of celiac disease in childhood and its benign course could help in the understanding of the underlying pathogenic mechanisms. We are grateful to Professor Angela Vincent (Oxford) for her helpful suggestions in reviewing the manuscript.
examined using a rating scale for the examination of frontal release signs (FRSS), with nine operationally defined items, each on a seven point semiquantitative scale. The nine reflexes were paratonia and palapomental, hand grasp, foot grasp, glabellar, rooting, snout, sucking (tactile), and sucking (visual).

Neuropsychological measures included the assessment of frontal lobe function (trailmaking tests A and B, behavioural dyscontrol scale, and the controlled word association test) and generalised cognitive impairment (CAMCOG). Depression was assessed using the Hamilton rating scale for depression, 15 item geriatric depression scale, and diagnostic criteria for DSM IV major depressive disorder. Family history of depression, was to die, and suicidal ideation within the past year were also recorded, as were blood pressure and a checklist for chronic physical illness.

Table 1

| Primitive reflexes in patients with peripheral vascular disease (n=25) and controls (n=25) |
|---------------------------------|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                  | Hand grasp | Foot grasp | Glabellar | Palpomental | Paratonia  | Rooting | Snout | Sucking (tactile) | Sucking (visual) |
| U                               | 0.15       | 0.01*      | 0.15      | 0.29        | 0.01*      | 0.44    | 0.08  | 0.30             |                 |
| pValue                          | 274.0      | 312.5      | 199.5     | 287.5       | 287.0      | 235.5   | 287.5 | 261.0            | 287.5           |

*Higher mean score in people with peripheral vascular disease.

Small numbers of patients, which may also have observed 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 concomitant disruption of fronto-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.


**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 presentation the patient’s wife had twice found him, incoherently, 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 exsmoker with hypercholesterolaemia and peripheral vascular disease which had been treated by a left femoral angioplasty 3 years earlier. The angioplasty was complicated by the occurrence of a pseudoaneurysm to be related to dye injection, and phenytoin had been prescribed for a short time thereaf- ter. 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 patient 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 pattern (figure A). 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). What was asked to bilateral somesthesia was also significantly impaired (figure B). What was asked to bilateral somesthesia was also significantly impaired (figure B). 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 hemianopop sia to confrontation testing but was otherwise normal, including bilaterally symmetric op- tokinetic 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 markable.

Brain CT and MRI, CSF examination, and routine EEG were normal. Routine haemato logical and metabolic analyses plus erythrocyte sedimentation rate, serum lactate, protein, and glucose, and urinalysis were unremarkable, as were thyroid function tests and TSH. Cardiac investigations to date had been normal, including ECG and echocardiogram. An attempt at the patient’s carotid Doppler studies was unsuccessful, and the patient was transferred to this hospital 10 days later. Hemiplegia unchanged, for possible angiography and further investigations.
density lipoprotein (3.92 mmol/l) and triglycerides (4.30 mmol/l) and low high density lipoprotein (0.73 mmol/l). Serum phenytoin concentration was therapeutic at 74 mmol/l. An ECG was normal.

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

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

A formal neuropsychological assessment performed in hospital documented impaired attention, concentration, and working memory, as well as several atypical calculation and spelling errors, the second involving unusual “near miss” letter substitutions or reversals (for example, “annexy”, “execuitive”). The formal testing identified no consistent evidence of visuospatial deficits or constructional apraxia. The findings were interpreted as inconsistent with the patient’s history but the possibility of a factitious aetiology was left open. A formal neuropsychological examination disclosed left lower facial droop, decreased left corneal and gag reflexes, and absent superficial abdominal sensation. The left lower limb revealed weakness and decreased sensation on the left side. Forced choice senso-

sory testing of finger and arm movement on the left demonstrated performance to be worse than chance (68% wrong choices). Motor bulk, tone, and reflexes were symmet-
rictic and plantar responses downgoing. He drew a clock normally at the 1 year follow up.

The clinical and laboratory findings de-
scribed 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 defini-
tively proved.

The inability to copy line drawings or to
draw a clock is, from a neuropsychologist’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 symp-
tomatology 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 sup-
port a diagnosis of malingering. Nevertheless, classification as a factitious dis-
order 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, how-
ever, no evidence could be gathered from the patient to support this speculation.

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2 Fragatano G, Amin K. Digit memory test: unequivocal cerebral dysfunction and sus-


Anosognosia and mania associated with right thalamic haemorrhage

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

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

On admission he was described as “bellig-

erent,” “agitated,” and “confused.” Blood pressure was 240/160. Neurological exam-
ination disclosed left lower facial droop, decreased left corneal and gag reflexes, and left hemiparesis with dense sensory deficits. With increasing obtundation, the patient was transferred to the intensive care unit and intubated. Brain MRI showed a large, left sided, hyperacute thalamic bleed with mass effect and oedema. The patient was extu-

bated 2 days later and 4 days after the stroke he was described as being drowsy and inattentive, but was able to answer questions.
appropriately. Neurological examination showed contralateral gaze preference, supra-nuclear vertical gaze palsy, difficulty converging, left sided flaccid hemiparesis, and dense, left sided hemianesthesia. Deep tendon reflexes were absent on the left and Babinski's reflex was seen on the left. 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 extubated, 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 frequently observed to the nurses’ attention 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, and could be consciously recalled by him, 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 after stroke the 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 function. This patient was showing, 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 becoming 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, with a recent oscillation with female staff and boasting of having fathered 46 children. His girlfriend was surprised when he kissed her in front of the staff because he had never previously shown affection before. He reported excellent energy and expansively invited all of the staff to his home for thanksgiving. Sleep was not disrupted or reduced and he had a good appetite. When beginning to acknowledge his left sided weakness, he remained blissfully unconcerned. He scored 31 points on a mania rating scale,1 which was well in the manic range. The mania resolved gradually over a 10 week period after stroke. Other than alcoholism, the patient had no history of psychiatric illness and there was no family history of psychiatric illness. The patient had not seen a physician in many years. Visual acuity was found to be reduced to 20/200, with poor reading ability, impaired confrontation naming, and impaired performance on a verbal task of fluency and initiation. Auditory comprehension was mildly impaired. Vocabulary 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 performance remained intact. His initial recall of two paragraphs scored formally within the low 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 hemorrage with mass effect and oedema, with oedema extending into the cerebral peduncle. The degree of swelling was consistent with deoxyhaemoglobin. Also present was increased T2 signal bilaterally in the basal ganglia, moderate cerebellar atrophy and mildly to moderately prominent of the frontal cortical sulci compatible with cerebral atrophy.

Functional MRI performed 44 days after the stroke demonstrated a 2 cm right thalamic haematoma. Functional MRI performed the same day demonstrated a 2 cm area of absent cerebral blood volume at the posterior margin of the right thalamus without any evidence of decreased cerebral blood volume within the right parietal, frontal, or temporal cortex.

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, when Babinski1 introduced the term anosognosia he noted as one of his examples a case in which the patient, thought of as anosognosic, 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 Kahn9 noted that euphoria was common in patients with anosognosia. Moreover, although Cutting11 emphasised that apathy is the mood most 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 aetologically 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 in ownership and disbelief 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 insight.

Several explanations have been proposed to explain the phenomenon of anosognosia. All the models invoke dysfunction of the cerebral cortex, especially the parietal area, which is interesting since in this case functional MRI failed to demonstrate decreased CBV in the parietal lobe.

In summary, we present a case of mania accompanying anosognosia in a patient with a large 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 arrest

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 epileptiform seizure activity. After changes to antiepileptic medication and the insertion of a permanent cardiac pace maker he has had no further episodes. In cases of epileptic cardiac dysrhythmia, isolated EEG or ECG 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 lost.

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

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

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

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

Cardiovascular and neurological 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. Interictally rare spikes were seen over the right hemisphere, while he was an inpatient but they were normal. No episodes were witnessed. EEG recordings were normal, 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 a history of respiratory failure and proximal muscle weakness as prominent features.

The patient started to have dyspnoea 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 Tokyo Red Cross Hospital as an emergency patient with a coma due to CO2 narcosis (PCO2 117.6, PO2 64.0). Responding to mechanical ventilatory support, he completely recovered consciousness within a day. His respiratory condition in the daytime improved to that previously. However, he needed mechanical ventilation during sleep because of nocturnal hypventilation.

The patient had no history of diabetes mellitus, pulmonary or neuromuscular disorders. 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 palseies 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 and mild weakness of the pelvic girdle was found. The muscular atrophy was prominent in the shoulder girdle, intercostal muscles, paravertebral muscles, and pelvic girdle, and moderate atrophy was present in all four limbs (figure). There was marked weakness of the shoulder and pelvic girdle and mild weakness of the distal limbs. The thorax showed poor respiratory movement, and the patient showed paradoxical movement of the abdomen in the supine position. Tendon reflexes were hyporeactive in all limbs. The patient’s sensations of touch and pain were mildly impaired in the four limbs on the right side. Plantar reflexes were normal. His vital capacity was 1.9 l (55% of the normal mean) in the sitting position, but 1.3 l (38%) in the supine position. The percentage of forced expiratory volume in 1 second was normal. 99% of the exercise electrocardiography 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 antibodies 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 m/s [normal <3.6]) nerves, and moderate decreased conduction velocities in the right median (35 m/s [normal >50]), ulnar (45 m/s [normal >40]), 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 in the right phrenic nerve was slightly increased.
delayed (8.7 ms (normal<8.0)). Sensory nerve conduction studies showed a reduced amplitude of sensory nerve action potentials and conduction slowing in all the nerves tested. Electromyography carried out in the supraspinatus, deltoid, biceps, flexor carpi ulnaris, brachioradialis, quadriceps femoris, biceps femoris, tibialis anterior, and gastrocnemius muscles showed polyphasic motor unit potentials of long duration, but denervation potentials were rare. A left sural nerve biopsy showed scattered tomaculous thickening of the myelin sheath and some abnormally thin axonal myelin sheaths. The density of myelinated fibres was reduced (5726/mm²). A gene analysis disclosed a 53% gene dose of PMP-22 related to normal controls, using Southern blots of DNA digested with EcoRI. Given the possibility of superimposing demyelinating neuropathy, especially chronic inflammatory demyelinating polyneuropathy, oral prednisolone (60 mg/day) was given for 1 month. However, the patient’s clinical condition did not respond to this treatment. Pulmonary dysfunction and proximal muscle weakness were almost steady during the next 3 years.

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

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

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

Spinal accessory neuropathy and internal jugular thrombosis after carotid endarterectomy

Spinal accessory neuropathy is a rare complication of carotid endarterectomy (CEA). 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 underestimated in many cases.1 Concurrent ipsilateral spinal accessory neuropathy and internal jugular venous thrombosis after CEA is expected to be rare, and this is underscored by the lack of published cases. Despite this apparent rarity, a common pathogenetic mechanism for postoperative spinal accessory neuropathy and internal jugular venous thrombosis may well be present, at least in some cases, which may lead to the consideration of the possibility of both when either is discovered.

We report on a patient who developed right spinal accessory neuropathy and internal jugular venous thrombosis after right CEA. A 59 year old man underwent right CEA for possibly symptomatic stenosis. Angiography had shown 90% stenosis of the right internal carotid. The operation was done under general anaesthesia. The carotid bifurcation was unusually distal, necessitating a long dissection and high retraction. No immediate postoperative complications were evident. The next day, the patient complained of mild pain at the operative site, but did not notice any weakness. The pain spread into his right shoulder within several days; at that time, he also noted difficulty raising his right arm. His symptoms worsened further a few weeks later, 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 spinal accessory neuropathy with minor denervation of the right accessory nerve. 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 electrophysiological studies were consistent with chronic right spinal accessory neuropathy, and repeat ultrasonography showed persistent right internal jugular venous thrombosis.

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

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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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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. Oculovestibular 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 normalization of the displacement of the brain stem.
decreased on the left side. Furthermore, there was mild left dysladiochokinesia. Neurography of the facial nerve was normal on both sides. Needle myography of the left frontalis and orbiculari oculi did not show signs of denervation.

An MRI study showed a large gadolinium enhancing tumour within the left cerebellar-pontine angle extending to the cavaux Meckelii with marked displacement of the brainstem to the contralateral side (figure A and B). Cerebral angiography showed a discrete blush of the tumour as typically seen in meningo- 

The tumour was totally removed by a combined transtemporal supratentorial and infratentorial presigmoidal approach. The postoperative course was uneventful and there were no new deficits. The facial palsy improved slightly as well as the trigeminal hypoesthesia. Audiometry remained unchanged. Postoperative imaging showed no residual tumour and the displacement of the brain stem within the posterior fossa had resolved (figure C). Marked improvement of the left sided craniofacial dyskinesias occurred during the next weeks.

The postoperative improvement of the dystonic and choreic grimacing and the cervical dystonia indicates a causal association between the petroclival meningioma and the segmental hyperkinetic movement disorders. Such a rela-

tion is supported also by the absence of a fami-

liy 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. Hemifacial spasm was seen in patients with paroxysmal neuromuscular, myasthenia, and epidermoid tumours of the cerebel-

lone angle. Acoustic neuromas and anaplastic pontocerebellar glioma can be asso-

ciated with facial myokymia and spastic parietic facial contracture.1 Also, cervical dystonia due to tumours of the cerebellopontine angle have been reported recently.1


Acute multifocal cerebral white matter lesions during transfer factor therapy

Transfer factor is an active substance of unknown structure present in dialysable leu-

cocyte extract which is assumed to transfer cell mediated immunity in an antigen specific fashion.2 The mechanisms of action of trans-

fer factor are still far from clear; in vitro dialys-

able leucocyte extract increases macro-

phage activation and interleukin (IL) 1 production and enhances leucocyte chemo-

taxis and natural killer function. Transfer fac-

tor has been reported to stimulate the cell mediated antigen specific response in patients with various infections3; therefore, treatment with transfer factor has been suggested in patients with selective deficits in cell medi-

ated immunity such as refractory neoplasms and chronic infections. Moreover, it has been used in the treatment of uveitis.4 Administration of dialysable leucocyte ex-

tract has to be free of hypersensitivity, long lasting side effects, or complications, except for transitory hyperpyrexia.5

We report on a patient in whom multiple cerebral white matter lesions developed after transfer of dialysable leucocyte extract orally for uveitis. A 28 year old man was admitted to hospital because of headache, mental confu-

sion, and right hemiparesis. He had had recur-

rent bilateral uveitis from the age of 12 to 14 with relapse of 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 gen-

eralised 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 for which the Babinski’s sign.

Our case provides further evidence that functional impairment by compression and distortion of the brain stem may cause hyper-

kinetic cervicofacial movement disorders. It is supported also by the fact that movement disorders are accessible to surgical treatment of the underlying pathology. Therefore, pa-

patients with cranial or cervical dystonia or choreic dyskinesia should undergo MRI imag-

ing to rule out a surgically treatable cause.

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tracture as the result of anaplastic pontono-


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Axial T1 weighted image after contrast administration showing multiple focal lesions in the periventricular white matter and left central semiovais exhibiting thick annular enhancement.


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eralised 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 for which the Babinski’s sign. No fever or meningismus were present.

Laboratory examinations on admission showed slightly increased deep tendon re-

dexes on the right side and was normal 40 days later; all laboratory analyses were normal except for antistreptolysin tites (265 UI/ml). Two MR scans at 1 and 4 months after onset showed progressive reduction of lesions without contrast enhancement but a new large lesion in the left occipital white matter, which showed moder-
ate 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 moder-
ate 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 as-

sumption 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 muscle, and antineutrophil cytoplasmic anti-

bodies, lupus anticoagulants, cryoglobulins, immune complexes, complement fractions, and neoplastic markers.

Seralogical investigations showed IgG but not IgM against cytomegalovirus (CMV), Herpes simplex, Varicella zoster, Epstein-Barr virus, Coxsackie, Adenovirus, Enterovirus or Borrelia burgdorferi were present. Polymerase chain reaction search for Herpes simplex 1 and 2, Varicella zoster, CMV, Epstein- Barr virus, and JC virus in the CSF was negative.

Cell, protein, and glucose concentrations in CSF were normal. No oligoclonal bands or antibody against CMV, Herpes simplex, Varicella zoster, Epstein-Barr virus, Coxsackie, Adenovirus, Enterovirus or Borrelia burgdorferi were present. Polymerase chain reaction search for Herpes simplex 1 and 2, Varicella zoster, CMV, Epstein- Barr virus, and JC virus in the CSF was negative.

Brain MRI showed several extensive asym-

metric lesions in the subcortical and periventricular cerebral white matter, some of which exerted a mass effect on the nearby CSF spaces. All lesions exhibited thick ring-like enhancement after intravenous contrast admin-
istration (figure). The brain stem, cere-

bellum, and cervical spinal cord were spared.

The patient had a progressive spontaneous remission of symptoms and signs. The neurological examination 20 days after onset showed slightly increased deep tendon re-

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bodies, lupus anticoagulants, cryoglobulins, immune complexes, complement fractions, and neoplastic markers.
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 pathogenic mechanisms underlying the triggering, development, and duration of multiple sclerosis and acute disseminated encephalitis are still far from clear despite the progress made in unravelling them. Some findings suggest that acute disseminated encephalitis and multiple sclerosis lie at the two poles of an autoimmune range, in which autoantigen reactivity is only temporary and direct against a single antigen in acute disseminated encephalitis and multiple antigens in multiple sclerosis. Although the hypothesis that dialysable leucocyte extract had triggered an autoimmune disorder in our patient cannot be proved, our finding is in line with the report of multiple cerebral lesions after therapy with interleukin-2. As already noted, dialysable leucocyte extract contained in vaccines) and various foreign substances such as during vaccinations or viral infections had 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.

**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 rolled instead of crawling. He walked at 15 months, spoke at 2 years with poor articulation, and still speaks in short, unelaborated sentences. His social and language development laggard 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 imprecision of fine finger movements, dysgraphaesthesia on sensory testing, and a manieristic gripping handshake. There were no extrapyramidal movements, dysgraphaesthesia on sensory testing, and a manieristic gripping handshake. There were no extrapyramidal movements, dysgraphaesthesia on sensory testing, and a manieristic gripping handshake. There were no extrapyramidal movements, dysgraphaesthesia on sensory testing, and a manieristic gripping handshake. There were no extrapyramidal movements, dysgraphaesthesia on sensory testing, and a manieristic gripping handshake. There were no extrapyramidal
symptoms. His IQ score was in the low range (WAIS-C=55 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 other people’s 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. Psychometric 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 behaviour. 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). SPECT showed increased activity in 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 0.70–1.45 mM), ionised calcium was 0.80 mM at pH 7.4 (normal 1.10–1.34 mM); urinary calcium was 0.8 mM (normal 2.5–6.3 mM). Serum parathyroid hormone was below 0.6 (normal 1.0–6.55 µM), and a nuclear scan of the parathyroid glands showed an absence of activity. With a combination of vitamin (normal 1.0–6.55 µM/l), and a nuclear scan calcium was 0.8 mM (normal 2.5–6.3 mM). pH 7.4 (normal 1.19–1.34 mM/l); urinary 1.5 mM/l). Ionised calcium was 0.80 mM/l at the upper cervical spinal cord (figure). The laboratory tests were normal, confirming the absence of rheumatoid arthritis, metabolic disease, or gout. Surgical removal via a transoral approach with a minimal bony resection was direct and provided sufficient space to obtain spinal cord decompression. It was followed by a posterior Cl–C2 fusion. Macroscopically, the lesion had no capsule and resembled a hypertrophic laminmentum flavum. Microscopically, it was non-inflammatory, hypocellular, and ligamentary pieces found within the mass appeared fibrous and almost disintegrated. The patient regained normal neurological function. Over a 3 year follow up period there was no recurrence.

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

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

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

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

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We focus attention on hypertrophic atlantoaxial ligamentary disease as a degenerative disease that must be considered within the possible causes of high spinal cord compression.
Selective hemihypesthesia 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 reflexes, were normal. The patient's only complaints were left temporal headache and right hemihypesthesia.

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

The loss of pain and temperature sensation improved gradually and the patient was discharged 2 weeks later. T2 weighted images 1 month later showed a more localised lesion in the same area. The coronal slices showed a high intensity lesion at the level of lower midbrain coinciding with the tentorium 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 craniovascular injury. Responsible lesions for sensory impairment, detectable by neuroimaging studies, almost always accompany associated neurological deficits. To our knowledge, a selective injury at the spinothalamic or trigeminothalamic tracts due to the midbrain; however, due to the proximity of the tentorial edge to the midbrain on the injured side, tentorial contact to the midbrain supposedly occurred more readily. Brain MRI findings support the anatomical features of this tentorial coup injury. This injury is not rare in patients with severe head injury, accompanied by other intracranial lesions, and is often caused by lateral displacement of the brain stem relative to the tentorium. It is influenced by congenital variations in the size and shape of the tentorial incisura.

The brain stem of the patient with a narrow incisura is more vulnerable to the direct contusive effects than that of a patient with a wider incisura. Therefore, even in minor head injury, this mechanism may occur in patients preconditioined with narrow tentorial incisura, which may have been the case in our patient.

The concept of tentorial coup injury against the midbrain is not new. It usually accompanies various degrees of conscious disturbance and other long tract signs, sensory deficits as well as cerebellar and cranial nerve palsies due to the midbrain lesion or other associated intracranial lesions. The clinical manifestation of our patient may represent one of the mildest forms of the midbrain contusion. The possibility 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.

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

The mechanism of midbrain injury in our patient was speculated to be due to tentorial coup injury based on MR images. The location of contusion was at the lower dorsolateral midbrain, coinciding with the tentorial edge level. Initiation of injury was the surface of the midbrain; however, due to the proximity of the tentorial edge to the midbrain on the injured side, tentorial contact to the midbrain supposedly occurred more readily. Brain MRI findings support the anatomical features of this tentorial coup injury. This injury is not rare in patients with severe head injury, accompanied by other intracranial lesions, and is often caused by lateral displacement of the brain stem relative to the tentorium. It is influenced by congenital variation in the size and shape of the tentorial incisura.

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CORRESPONDENCE

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 \( \gamma \)-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.\(^1\) Degeneration of certain cerebellar pathways is probably responsible for the loss of this dopaminergic innervation.\(^2\) Dopamine agonists could therefore be of potential interest in the treatment of toluene induced tremor. This hypothesis was explored in a recently described case,\(^3\) which showed remarkable clinical and iconographic 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 abstinence from inhalant misuse, and (d) mild cerebral atrophy and marked low signal intensity in globus pallidi, thalami, red nuclei, and substantia nigrae 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 associated with heredodegenerative disorders in which the dentato-rubro-olivary system is affected. In addition, there is evidence that catecholaminergic pathways are also involved in this type of ataxias, supported by loss of dopaminergic neurons of these neurotransmitters in the CSF of patients with heredodegenerative ataxias.\(^4\) 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) which resulted in relapse of the tremor and ataxia. The response of this patient (our second case) supports the potential interest of amantadine hydrochloride in the treatment of toluene induced tremor and ataxia. Further cases will be of potential interest in the treatment of heredodegenerative ataxias, such as the one described by Miyagi et al.

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 children with 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 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 then had been further selected by virtue of having had at least 3 years tertiary centre follow up and needing two MR scans of the head. The prevalence of astrocytomas and risk factors, and hence the positive predictive value of any screening tool in a general population of patients with tuberous sclerosis complex is likely to be different from those described in the highly selected group studied in this paper.

The second is that the authors have made a potentially misleading decision to exclude more than half their study sample because they do not have lesions close to the foramen of Monroe. It is not certain that all SEGAs arise from lesions close to the foramen. They may arise in the fourth ventricle. Furthermore, the late presentation of many lesions in the lateral ventricles has, in the past, precluded accurate determination of their point of origin. A study selects 24 of 60 patients who had met their entry criteria but does not state how many of the excluded patients had no subependymal nodules or nodules that were not “near the foramen of Monroe”. Inclusion of this group 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 test) between the outcome and both of these explanatory variables.

Identifying the risk factors that can tell us which subependymal nodules will become invasive is important. As subependymal nodules and SEGAs seem to be histologically identical it is unlikely that pathologists will provide an answer. The study of Nabbout et al suggests some risk factors and also identifies some other factors in toluene induced tremor and ataxia which may be of potential interest in the treatment of heredodegenerative ataxias.

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 “flip 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 ALS in 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 to describe this form of ALS have been danging arm syndrome, suspended form, orangutan sign, dead arm sign, bifacial palsy, rizomelic amyotrophy, and the idea of naming it a distinctive phenotype of a neurogenic syndromic amyotrophy in children with tuberous sclerosis.
At the initial stages of the illness, there is no ambulatory ability, albeit with gait disorders, clinical course, in that they usually preserve survival of 57 months compared with 39 months. (2) The age of onset of this form constituted 10% of the ALS group as a whole (n=395). (3) The prevalence of this form of ALS was 3:1 in our study, and a predominance among men (the male/female ratio was 9:1 in this form, compared with 3:1 in the total ALS group), (4) The age of onset of the median survival (a median survival of 57 months compared with 39 months in the total 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.

On a personal level, we also note two findings characteristic of these patients. In the initial stages of the illness, there is no effect on the diaphragm and the respiratory muscle failure occurs much later than in the typical form of ALS. This can be seen in the follow-up of the results obtained in the respiratory function tests (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 deltoides (especially infraspinatus) and a loss of strength in the external rotation of the shoulder (infraepastrap, supraespaspinus, and teres minor). As a consequence, the upper limbs adopt a characteristic position, with the shoulders slumped, and the arms, forearms, and hands in pronation.

The atrophy and weakness of the infraspinastrap and the supraespaspinus, 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 the cervical spondylisis and ALS can cause difficulty in diagnosis. The problem lies in the fact that cervical spondylisis is a common condition. It is found in 83.5% of men and 80.7% of women over the age of 35. 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.

Isolated dysarthria

We read with interest the article by Urban et al. Using transcranial magnetic stimulation, the authors demonstrated electrophysiologically evidence for a central monophasic of the tongue in patients with isolated dysarthria from stroke.1 As in their patients transcranial magnetic stimulation induced absent or delayed corticobulbar responses at the tongue, the authors ascribed isolated dysarthria to interruption of the corticobulbar pathway involving the thalamocortical and corticostriatal fibres as well as the corticobulbar fibres. In fact, lacunar infarcts around the internal capsule-corona radiata are likely to underlie this ascending and descending dysfunction.

To assess corticopontocerebellar tract function, Urban et al investigated cerebellar blood flow in patients with isolated dysarthria using HMPAO-SPECT. They concluded that the corticopontocerebellar tract is preserved 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. In our study, we showed that the corticopontocerebellar tract is preserved 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. In our study, we showed that the corticopontocerebellar tract is preserved isolated dysarthria because of no evidence for cerebellar diaschisis on SPECT.
lution with a dyskinetic rating scale, had a more advanced stage of the disease possibly with coexisting dystonia or rigidity. These assertions deserve some comments.

The mean disease duration of our nine patients with Huntington’s disease was 6.2 (4.1) years which is actually shorter than the duration of the six patients reported by Hanajima et al. (8.3 (5.9) years). Most of our patients could be considered in an early stage of the disease, the Unified Huntington’s disease rating scale, and none presented dystonia, rigidity, or any other additional movement disorder. In this regard, however, it should be pointed out that bradykinesia is often associated with chorea in patients with Huntington’s disease¹ and may even precede the appearance of choreic dyskinesia.² Chorea itself is often reduced in the more advanced Huntington’s disease stages.³ It is unlikely, therefore, that any neurorophysiological approach can test purely chorea even in the early Huntington’s disease stages. In addition, different mechanisms are involved in Huntington’s disease and other choreas as suggested by the lack of impact of somatosensory evoked responses and long latency stretch reflexes in the second.⁴

We were not really surprised at the results of Hanajima et al. as we do share their opinion that patients with Huntington’s disease may be characterised by large individual differences in the involvement of motor cortical areas. Actually, three patients in our study showed an amount of intracortical inhibition within the confidence limits of the control population. We also think that the impairment of intracortical inhibition is likely to develop during the disease progression as we did not find any change in four patients, two of them already reported, with positive DNA testing but completely asymptomatic.

The discrepancies between the two studies are more likely to be explained, at least in part, by some methodological differences. For instance, the amplitude of the control response was larger in our set (approximately 1.0 mV compared with 0.5 mV in the study of Hanajima et al.). This may induce a different sensibility 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 pathophysiological 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.⁵ 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.

The authors reply:

We were very grateful for the response of Abbruzzese et al to our paper. We completely agree with their opinions.

The discrepancy between the two studies⁶ 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 number.

We may have to take CAG repeat number into consideration in comparisons. Unfortunately, however, we have no way to do such comparisons between these two studies. We could say, at least, that the mean intracortical inhibition was normal even at the same stage of the disease as that of the patients of Abbruzzese et al., if studied with our method.

We also consider that pathophysiological 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 stimulations. Therefore, we used the intensities of the conditioning stimulus before we confirmed inhibition in studies of patients.⁷ We used an intensity of 5% less than the active threshold as a conditioning stimulus, a facilitatory effect must often superimpose on the intracortical inhibition. This makes the interpretation difficult. Was the intensity of 80% of the resting threshold below the active threshold in their patients? In our experience, 80% of the resting threshold was sometimes above the active threshold. These factors must be considered in interpreting the results of paired magnetic stimulation.

Such a methodological problem is inherent in human studies because we have no direct way of detecting the threshold of the motor cortex. Our two results must be true. We may have two completely different interpretations of these results. (1) The intracortical inhibition is normal in Huntington’s disease. Abbruzzese et al showed the reduced inhibition because they used a high intensity conditioning stimulus with which the degree of

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 these results we previously found⁸ 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 studies⁹ are due to differences in patient selection as they included patients with early stage Huntington’s disease to “study the pathophysiology of chorea unaffected by other disorders movement.”¹⁰ They postulated that our cases, because of the reported corre-
intracortical inhibition is often decreased even in normal subjects. The 80% of the threshold for relaxed muscles must correspond to different values relative to the threshold for active muscles in patients from that in normal subjects. (2) The intracortical inhibition is dependent on FV and the level of 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. Which ever is true, the intracortical inhibition must be normal or slightly disturbed in Huntington's disease.

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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. I see problems both with the theoretical foundation of their CCP concept and with the interpretation of their results.

Firstly, the physiological meaning of both formulae of CCP presented (CCP1 and CCP2, respectively) is questionable. The implication of both presented equations is that the instantaneous value of cerebral blood flow velocity (FV(t)) at a given moment t is equal to the arterial blood pressure at the given time (ABP(t)) minus CCP divided by cerebrovascular resistance (CVR):

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

(1)

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

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

(2)

Inserting equations 2 and 3 into the frequency domain equation for CCP of the authors:

\[ \text{CCP2} = \text{ABP}-\text{A1}/\text{F1} \]

(4)

leads to

\[ \text{CCP2} = \frac{\text{ABP} - \text{CVR1}}{\text{CVR0}} \times \frac{\text{ABP} - \text{CVR1}}{\text{CVR0}} + \text{CVR1} \]

(5)

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

\[ \text{CCP2} = 0.5 \times \text{ABP} + 0.5 \times \text{CCP} \]

(6)

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

The second criticism concerns the correlation of the calculated CCP2 values with mean ABP found by the authors (p<0.5; p<0.05). According to the original idea of Burton, CCP represents a certain mean ABP value below which small vessels begin to collapse. CCP should, therefore, be a constant value independent of the actual ABP. On the other hand, this significant correlation can be explained by our equation 5, again indicating the missing physiological basis of the CCP concept of the authors.

Thirdly, it seems doubtful that CCP could be estimated using pressure and flow values from ABP ranges clearly above CCP and flow values clearly above zero flow, respectively. As long as small vessels do not collapse (ABP>CCP) it is not possible to decide whether their actual wall tension is determined more by transmural pressure or by active 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 hyperventilation). In the case of ABP<CCP and a small vessel collapse according to the model of the authors, CVR should increase towards 0 (ABP=0) and FVd 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 FV is more accurately given by cerebral perfusion pressure (CPP=ABP-ICP) than by ABP-CCP. Therefore, equation 2 changes to

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

(6)

and equation 5 to

\[ \text{CCP2} = \frac{\text{ABP} - \text{CVR1}}{\text{CVR0}} + \text{CVR1} \]

(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".

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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 injuries. 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:

\[ \text{CPP1} = \text{ABP} - \text{ABPpp} + \text{FVpp} \]

(8)

\[ \text{CPP1} = \text{ABP} - \text{ABPpp} + \text{FVpp} \]

(9)

(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 has been given in fig 1. CCP1 is an x intercept point of linear regression between subsequent systolic and diastolic values recorded within 6 second intervals of flow velocity (along y axis) and arterial pressure (along x axis). In fact, the formula proposed by Michel et al is very similar. The only difference is that instead of the original waveforms of FV and ABP, first (fundamental) harmonic components were taken for the same graphical construction—that is,

\[ \text{CCP2} = \text{ABP} - \text{A1}/\text{F1} \]

(10)

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 (as equation (1) implies), because the "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, CPP 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 of Fourier transform of "cerebrovascular admittance".

Definition of CVR0 as FV/(ABP-ICP) 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 031) and CVR1 0.972 (SD 0.29), the difference is not statistically significant. Therefore, the suggestion that the CVR1/CVR0 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 have never suggested anyone could do so.

The second criticism was that our CCP positively correlated with ABP. It should not be a surprise. When ABP decreases, vasodilatation occurs and arterial wall tension decreases. Therefore presupposing 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 him-
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.1 Levodopa induced dyskinasias are currently thought to share a similar pathophysiology2 but recent findings also suggest that abnormal patterns of neuronal firing in the globus pallidum internum may be as relevant.3 Data from both parkinsonian monkeys and patients with Parkinson's disease submitted to lesion4 or functional blockade of the subthalamic nucleus are in keeping with such a general principle, but the threshold to induce dyskinasias in the parkinsonian state is higher than in intact animals.4 The case recently described by Figueiras-Mendez et al1 is extremely interesting as it suggests that functional inhibition of the subthalamic nucleus by high frequency stimulation blocks levodopa induced dyskinesias. This is clearly at odds with the current pathophysiological model of the basal ganglia.5 Thus, the finding of Figueiras-Mendez et al1 raises the intriguing possibility that dyskinasias depend or are facilitated by a tonic (or functional) hyperactivity of the subthalamic nucleus: evidence for reduced levodopa induced dyskinesias only by reduction in levodopa intake.6 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 low threshold for dialling to the thalamus from the globus pallidum internum are placed dorsocaudally to the subthalamic nucleus and could be blocked by high frequency stimulation.7 When the recording electrodes were lowered caudally to the subthalamic nucleus in sagittal planes 11 mm or less, neuronal activity is characterised by action potentials of large amplitudes (0.5–1 mV) with a high background activity, 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 occasion the distinction may not be easy. Accordingly, it is very important to document in more detail the findings in the case of Figueiras-Mendez et al1. 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 measurement of the changes in the anatomy of the basal ganglia.

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2 Crossman AR. A hypothesis on the pathophysiology of the primate subthalamic nucleus result in transient dyskinasias in the lateral region of the subthalamic nucleus, where the sensorimotor region lies. A recent anatomical study6 also showed that the cortical-subthalamic nucleus connection 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.7 All this heterogeneity may have pathophysiological relevance, one aspect of which could be the findings in the patient reported by Figueiras-Mendez et al.1 How ever, before the findings of this case may be used to sustain a major change in the role of the subthalamic nucleus in the origin of levodopa induced dyskinasias, there is a crucial issue to resolve—namely, the location of the tip of the stimulation electrodes.

There are several points leading us to question the actual site of action of the electrode: (1) Stimulation of the subthalamic nucleus in Parkinson's disease has been associated with the production of dyskinasias only relieved by reduction in levodopa intake.8 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 low threshold for dialling to the thalamus from the globus pallidum internum are placed dorsocaudally to the subthalamic nucleus and could be blocked by high frequency stimulation.7 (2) When the recording electrodes were lowered caudally to the subthalamic nucleus in sagittal planes 11 mm or less, neuronal activity is characterised by action potentials of large amplitudes (0.5–1 mV) with a high background activity, 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 distinction may not be easy. Accordingly, it is very important to document in more detail the findings in the case of Figueiras-Mendez et al.1 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 measurement of the changes in the anatomy of the basal ganglia.


Figueiras-Mendez et al reply: We thank Obeso et al for their comments regarding our recent report.1 In summary, they raised some interesting points which need further clarification.

Recognition of the electrical activity of the subthalamic nucleus will be facilitated by different criteria: (a) high frequency discharge (25 Hz or higher) within the nucleus;2 (b) a tonic (regular), phasic (irregular) or a rhythmic pattern of discharge;3 (c) response to voluntary/passive movements.4,5 When rhythmic discharges were recorded irregular passive manipulations were performed or the patients asked to move the limbs irregularly;4 (d) response to tremor activity. Positive cells were so considered based on the criteria accepted with the EMG and the accelerometer recorded simultaneously. Artificial manual stoppage 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 units above the subthalamic zona incerta and zona incerta with proper somatotopical representations in the primate subthalamic and zona incerta with proper characteristics;6 (f) a change in the background basal noise when entering the subthalamic nucleus. A higher activity is observed; (g) the activity is observed when entering the subthalamic nucleus. A lower background noise level; (h) 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.7 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 levodopa induced dyskinesias 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 the subthalamic nucleus. A lower background noise level; (b) 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.7 All these points were fulfilled by the patient reported.

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

(c) Motor responses and tremor 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 fixed 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 voluntary movement 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 dismissed 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 was stimulated electrically. It was always tested in the surgery before cementing it and, only when the symptoms are considered, the final position of the electrode was chosen place. The final position of the electrode, assessed by ventriculography, was 12 mm for the right hemisphere, and 11.5 mm for the left hemisphere.

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Nitrino oxide in acute ischaemic stroke

The pivotal role of nitric oxide (NO) in cerebral ischaemia has been elegantly highlighted in the recent editorial by O’Mahony 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 the range of 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 and alter NO production 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 regulated endothelial NO in the brain without altering expression of neuronal NO. Recent findings also suggest that statin therapy influences the activity of inducible NO. Lovastatin has been shown to inhibit cytokine mediated upregulation of inducible NO and production of NO in rat astrocytes and macrophages, and this inhibition may represent a mechanism for suppressing inflammatory responses that accompany ischaemia. Most interestingly, these preliminary findings suggest that statin therapy may modify the familiar and unfriendly faces of brain NO in a synergistically neuroprotective manner. These and other vascular effects of statins in cerebral ischaemia are potentially of importance in human and ongoing studies such as the The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study3 will help clarify their role in human cerebrovascular disease.

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BOOK REVIEWS


That neuroinmunology 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 facing with a diagnostic conundrum and the experimental immunologist inquiring into the clinical relevance of his findings. At first sight it seems improbable that both of these goals might be achieved in one volume; this book however, succeeds admirably in what it sets out to do, as much as a result of its literary style as its content.

The intrusive authorial voice fell into disfavour in literary circles around the turn of the century because it was thought that calling attention to the act of narrating might detract from realistic illusion, so reducing the emotional intensity of what was being represented. It is a device much favoured by postmodern writers, who expose the nature of fictional constructs. The intrusive medical author never dropped out of fashion, although in these days of evidence based prejudice, authorial 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 immunological and inflammatory disorders of the Central 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 disease, with examination of syndromes of isolated demyelination, acute disseminated encephalomyelitis and allied conditions, and some of the syndromes of demyelination that are now accepted as part of the range of multiple sclerosis. The chapters on demyelinating disease are drawn to a close by a discussion of existing and experimental therapies for multiple sclerosis.

The book continues with chapters on paraneoplastic disorders of the CNS, stiff man syndrome, neurological complications of

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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 unify 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 (Moller), antioxidants, and radical scavengers (Rosler et al). I found the review by Reisberg et al on ontogenetic 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.

STROKE AND ALZHEIMER’S DISEASE. Edited by DIETER LEYEN, FLORENCE PASQUIER, and PHILIP SCHREITZEN. (Current Issues in Neurodegenerative Diseases Volume 9). (Pp 225). Published by Holland Academic Graphics, The Hague, 1998. ISBN 90-5560-061-9. 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. Ploughing through the 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 dementia, the arguments for a pure vascular dementia, the role of Alzheimer’s disease in the genesis of dementia after stroke, the contribution of white matter changes on neuroimaging to dementia, and finally a short section examining practical questions such as the management of stroke in patients with dementia.

Although comments of 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 underlying hypotrophy and recurrent lobar haemorrhages. Perhaps common genetic factors are responsible and here the APOE alleles are discussed. The comprehensive section on deep white matter lesions seeks to explain the connection further—and convinces the reader that there is still a lot which is not well understood. It is in this section particularly that illustrations are greatly missed. Brief mention is made of other conditions which may produce white matter changes and dementia such as CADASIL, cerebral lupus, and the primary antiphospholipid syndrome.

Some typographical errors and mistranslations detract a little 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.

HEALING STORIES—Narrative in Psychiatry and Psychotherapy. Edited by GLENN ROBERTS and JEREMY HOLMES. (Pp 226, £47.50). Published by Oxford University, Oxford, 1999 ISBN 0-19-262827-5. 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. Storytelling also constructs the understanding of observation, inference, motive, and consequence in a fashion that informs future action. Our experience of the world is constructed around such narratives. They define us as individuals, family members, professionals, and cultural groups.

This book is a series of essays on psychotherapy, psychiatry, and also medicine that sees the awareness and use of narrative in clinical practice as a construct that can both
are two very fine accounts of narrative in psychiatric literature should buy this book for this particular interest to community psychiatrists. I would recommend because some aspects of the practical management of violence are missing—for example, a documented risk-benefit analysis, good failsafe communication, or deciding when to detain. One of the last chapters is a very good account of the management of hyperactivity in childhood, with good practical advice on the use of methylenedate.

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

SIMON FLEMINGER


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

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

There are a few cavils. The section on treatment of anxiety is skimpy (one and a half pages) compared with the treatment of affective illness (22 pages) or schizophrenia (59 pages). The brevity is only explained by the undeveloped state of that particular area of psychopharmacology. Sections on common side effects and indications for lumbar puncture and indications for EEG seem to have been displaced from some other primer for busy junior doctors. There is no index.

These quibbles apart, prescribing guidelines can be wholeheartedly recommended.

BRIAN TOONE


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

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

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

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