LETTERS TO THE EDITOR

Postictal psychosis related regional cerebral hyperperfusion

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

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 Antiepileptic drugs were withdrawn to facilitate seizure recording.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

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

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

Both patients showed postictal psychosis and had a regional increase in rCBF over the right temporal neocortex and the left basal ganglia compared with their interictal study (figure). Quantitative analysis for patient 1 showed changes of ASI during IP and PP over right MT was +75% (6.64676 to 1.652898); over the right LT was +116.78% (1.07927 to 12.55764); and over the left BG was +206.8% (2.07373 to 2.21574). Quantitative analysis for patient 2 showed changes of ASI during IP and PP over right MT was −8.8% (13.14217 to 12.64158); over right LT was +178.6% (10.4696 to 18.70577); and over left BG was +155.9% (5.85556 to 3.27522).

Postictal psychosis is a distinct clinical event associated with temporal lobe epilepsy.7 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 classical ictal event and partial seizures were precipitated by abrupt withdrawal of antiepileptic drugs.7 The cluster occurs in patients with poor drug compliance or during video EEG telemetry studies when antiepileptic drugs are being discontinued purposefully. The clinical course of postictal psychosis is usually benign and predictable.7 In our patients, the duration of psychotic disturbances lasted for 2 to 3 days, which is in keeping with the good prognosis. Antipsychotic drugs, such as haloperidol and fluphenazine are usually prescribed.7

The underlying mechanism of postictal psychosis is unknown. Postictal cerebral hypofusion has been postulated as an analogue to Todd’s paralysis after seizure.8 However, the presence of increased rCBF during postictal psychosis, may suggest an alternative explanation as ictal SPECT has been shown to be highly sensitive and specific in demonstrating seizure foci.9 To conclude, our results are contradictory to the hypofusion theory of Todd’s paralysis in postictal psychosis. We think that the hyperperfusion areas are responsible for the postictal psychosis. Further serial studies with cerebral SPECT or PET may enhance our understanding on the mechanism of postictal psychosis.

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

<table>
<thead>
<tr>
<th>Anti-FN mAb</th>
<th>Anti-TN Ab fragments</th>
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<tr>
<td><strong>Reco</strong></td>
<td><strong>Rec</strong></td>
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<tr>
<td><strong>ised isoforms</strong></td>
<td><strong>forms</strong></td>
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<tr>
<td><strong>Total TN</strong></td>
<td><strong>Total TN</strong></td>
</tr>
<tr>
<td><strong>Distribution of the isoform (n)</strong></td>
<td><strong>Widespread</strong></td>
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<tr>
<td><strong>Widespread</strong></td>
<td><strong>Present in adult tissues</strong></td>
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<td><strong>Present in the vascular wall and the matrix of fetal tissues and tumours</strong></td>
<td><strong>Present in the vascular wall and the matrix of fetal tissues and tumours</strong></td>
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Previous findings showed that ED-B+FN presents with conformational modifications in its central part and results from deregulation of FN pre-mRNA. The distribution of this isoform was found to be highly restricted in normal adult tissues. By contrast, ED-B+FN exhibited widespread distribution in the vasculature of fetal tissues, including brain, and of several types of malignancies. It was therefore regarded as a marker of angiogenesis.

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

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

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

The present findings indicate that 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 indicate 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.

This study was partially supported by the National Research Council (CNR), AIRC and the Ministry of University and Scientific Research (MURST). We thank Sergio Deseri, EE, for his technical help and Mr. Thomas Wiley for manuscript revision.

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 possibly requiring revision.

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 thyroiditis. This suggestion would certainly be consistent with the range of clinical presentations of other autoimmune cerebral vasculitides. As autoimmune thyroiditis is the commonest cause of hypothyroid failure in this country, it is likely to have been present in at least some of Asher's original cases. Although most had florid myxoedematous features at psychiatric presentation, this may simply reflect the diurnal variations of 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 had halted uncharacteristic behaviour. He had reported a vision of the crucifixion, and hearing the voice of his dead mother. He claimed that his house was occupied by the devil, drove around aimlessly in his car, and appeared constantly fearful and withdrawn. On the day of admission he had made a bonfire in the garden and burned his wife's clothes, family photographs, furniture, and business papers. When his wife and son tried to intervene he...
became aggressive and threatened them with a saw. The general practitioner was called and suspected an infective or a new psychosomatic disorder. 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 ability. He manifested behavioural changes, perceiving insects and mice moving through his visual field. Often, he expressed ideas of reference and delusions of persecution. He also manifested behavioural changes, perceiving insects and mice moving through his visual field. Often, he expressed ideas of reference and delusions of persecution. He also manifested behavioural changes, perceiving insects and mice moving through his visual field. Often, he expressed ideas of reference and delusions of persecution.
failing 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 con- vention, haematology, and sedimentation rates.

When a consequence of a noncerebral vascular pathology, alien hands can perform complex activities such as tearing clothes or undoing buttons. The description by MacGowan et al has characteristics of the callosal form (espe- cially 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.9 These authors described the alien limb as “involutionally 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 “she couldn’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 present- ing with an alien hand with or without myo- clonus.

We are indebted to Professor Eran Zardel, Depart- ment of Physiology, University of California, Los Angeles, USA

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 move- ment differ. In the callosal form, there are purposeful movements of the non-dominant hand. In the corticobasal form, there is grasp reflex and utilisation of the dominant hand. In the corticobasal degeneration, there are aimless movements of either hand.2 When a consequence of a noncerebral vascular pathology, alien hands can perform complex activities such as tearing 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.9 These authors described the alien limb as “involutionally 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 “she couldn’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).

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basic protein were not tested. Nerve conduc- tion studies were consistent with a predomi- nantly motor demyelinating peripheral neu- ropathy (table). Her symptoms improved spontaneoulsy 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 diminution 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 assessed by ELISA and IF were again negative. Nerve conduction 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- abilities 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 pre- viously reported. In the paediatric age group,

<table>
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<tr>
<th></th>
<th>1st Episode</th>
<th>2nd Episode</th>
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<tr>
<td><strong>Peroneal (µV)</strong></td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td><strong>Tibial (µV)</strong></td>
<td>74</td>
<td>70</td>
</tr>
<tr>
<td><strong>CMAP (µV)</strong></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>SCV (ms)</strong></td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td><strong>AMP (µV)</strong></td>
<td>16.2</td>
<td>16.8</td>
</tr>
</tbody>
</table>

MVC= motor conduction velocity; DL= distal latency; CMAP= compound motor action potential; SCV= sensory conduction velocity; AMP= amplitude; L=left; R=right.

In both episodes in the present case neuro- physiology was strongly supportive of a demyelinating peripheral neuropathy, which is most commonly attributed to a direct immune mediated attack to the myelin. By contrast, Wallerian and axonal degeneration may be caused by vasculitis, and nutritional, metabolic, and toxic factors.

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

It is known that in celiac disease many immunological perturbations can occur 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- lance, 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 possi- ble 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 the case shows two major issues: an acute polyneuropathy can be a complication of celiac disease in childhood and its benign course could help in the understanding of the underlying pathogenic mechanisms.

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Frontal release signs in older people with peripheral vascular disease

A growing body of research examining neurological aspects of clinically “silent” cerebrovascular disease suggests that neurologi- cal signs indicative of generalised organic brain damage may occur in the absence of completed stroke. These soft signs include primitive reflexes (frontal release signs), representing an anatomical and functional deaffer- entation of cortical from subcortical struc- tures. Primitive reflexes are known to occur in a wide variety of dementias, including Alzheimer’s disease and vascular dementia. It is likely that the presence of undetected cerebrovascular disease accompanying pe- ripheral vascular disease is underestimated, as peripheral vascular disease is known to be a risk factor for transient ischaemic attacks. A study assessing 373 older patients with peripheral vascular disease found that 72 of the 144 patients who had not experienced a transient ischaemic attack, or stroke signs, rep- resented a high risk of cerebrovascular disease.

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

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

A more detailed description of instruments is provided elsewhere. All subjects were
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 palpmomental, hand grasp, foot grasp, glabellar, rooting, snout, and visual/tactile sucking reflexes. Neuropsychological measures included the assessment of frontal lobe function (trailmaking tests A and B, behavioural dyscontrol scale, and the controlled word association test) and generalised cognitive impairment (CAMCOG). Depression was assessed using the Hamilton rating scale for depression, 15 item geriatric depression scale, and diagnostic criteria for DSM IV major depressive disorder. Family history of depression, stroke, to die, and suicidal ideation within the past year were also recorded, as were blood pressure and a checklist for chronic physical illness.

Full FRSS scores and scores on FRSS subscales were compared between groups using the Mann-Whitney U test for independent samples. In the peripheral vascular disease group, a correlation matrix for total FRSS score against DSMIV depression, CAMCOG score, generalised cognitive impairment and clinical depression was performed using Spearman's correlation coefficient. First, the relationship between the severity of physical and chronic illness, a subjective rating of the degree of severe illness, and that concomitant disruption of frontal/cerebral function may accompany peripheral vascular disease and that the predominant disruption of frontal/subcortical brain function may not present with hard neurological signs. As it is possible that silent brain infarction was present in patients with peripheral vascular disease, further studies incorporating brain imaging are required before there can be a clearer understanding of the relation between peripheral and central vascular pathology.

Table 1 Primitive reflexes in patients with peripheral vascular disease (n=25) and controls (n=25)

<table>
<thead>
<tr>
<th>Hand grasp</th>
<th>Foot grasp</th>
<th>Glabellar</th>
<th>Palmpomental</th>
<th>Paratonia</th>
<th>Rooting</th>
<th>Snout</th>
<th>Sucking (tactile)</th>
<th>Sucking (visual)</th>
</tr>
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<tbody>
<tr>
<td>U</td>
<td>274.0</td>
<td>312.5</td>
<td>199.5</td>
<td>287.5</td>
<td>287.0</td>
<td>235.5</td>
<td>287.5</td>
<td>261.0</td>
</tr>
<tr>
<td>pValue</td>
<td>0.15</td>
<td>1.0</td>
<td>0.001*</td>
<td>0.15</td>
<td>0.29</td>
<td>0.01*</td>
<td>0.44</td>
<td>0.08</td>
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*Higher mean score in people with peripheral vascular disease.

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

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

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**Facultious 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, inexplicably, 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 unchanging, for possible angiography and further investigations.

He was an ex-smoker with hypercholesterolaemia and peripheral vascular disease which had been treated by a left femoral angioplasty 5 years earlier. The angioplasty was complicated by the occurrence of an episode which was related to dye injection, and phenytoin had been prescribed for a short time thereafter. There was a remote history of heavy alcohol use, but he had been abstinent for several years. His father had had a stroke at the age of 65.

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

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

Cranial nerve examination suggested an incongruent and inconsistent left hemianopia to confrontation testing but was otherwise normal, including bilaterally symmetric optokinetic nystagmus. Motor examination showed paralysis of the left arm and leg, with bilaterally symmetric bulk, tone, and deep tendon reflexes. The plantar response was flexor bilaterally. Sensory examination showed decreased pinprick and absent light touch, joint position sense, and vibratory 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 unrevealing.

Brain CT and MRI, CSF examination, and routine EEG were normal. Routine haematological and metabolic analyses plus erythrocyte sedimentation rate, serum lactate, prothrombin time, partial thromboplastin time, and fibrinogen levels were normal. Fasting serum glucose, HbA1c, serum Ig survey, and thyroid stimulating hormone were all within normal limits. A hypercoagulability profile was negative. A lipid profile showed mild hyperlipidaemia with increased low
density lipoprotein (3.92 mmol/l) and triglycerides (4.30 mmol/l) and low high density lipoprotein (0.73 mmol/l). Serum phenytoin concentration was therapeutic at 74 µmol/l. An ECG was normal.

An ECG was normal.

An ECG was normal.

An ECG was normal.

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, “anxiety”, “executive”). The formal testing identified no consistent evidence of visuospatial deficits or constructional apraxia. The findings were interpreted as inconsistent with the patient’s history but the possibility of a factitious actiology was not specifically addressed—that is, tests designed to detect malingering during neuropsychological testing were not administered by the examiner, who had not been informed at the time of consultation of the presumptive neurological diagnosis of malinger ing or factitious disorder.

No further investigations were performed and the patient was transferred via the original hospital to a rehabilitation facility and subsequently discharged to home. Confronted with the findings of the video monitoring the patient appeared sanguine and accepting of the evidence that he should be able to move his left side. Six months later he was ambulatory but otherwise not significantly improved. He had been assessed by a psychiatrist but had refused psychiatric follow up, electing instead to be followed up by a psychologist. He understood his diagnosis and the need to stop using the left arm and leg but otherwise not significantly impaired. He was described as being drowsy and inattentive, but was able to answer questions about his work and was receiving disability funding. He walked with a limp favouring his left side and complained of persistent decreased sensation on the left side. Forced choice sensory 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 symmetric and plantar responses downgoing. He drew a clock normally at the 1 year follow up.

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

The inability to copy line drawings or to draw a clock is, from a 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.1 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 symptomatology just as he was scheduled for return to work after his first non-organic hemiplegic episode, and the intentionality required to feign poor clock drawing and constructional apraxia, there is much to support a diagnosis of malingering.1 Nevertheless, classification as a factitious disorder is at least as justifiable in view of the patient’s willingness to undergo medical investigations, including video monitoring.

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

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Anosognosia and mania associated with right thalamic haemorrhage

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

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

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

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

Four weeks after the stroke he first acknowledged that his left arm belonged to 
himself, and that it had been consciously recalled before otherwise. By this time he had a moderate 
hemiplegia and recognised “a little weak-
ness,” but continued to insist that he was well 
and able to return to work. By the 6th week as 
the patient more consistently 
acknowledged that he was weak on the left 
side of his body. A request for disabled hous-
ing “so that I won’t be a burden to my family” 
because he had never 
the stroke showed a2c mr right thalamic hae-
matoma. 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 evi-
dence 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 
Babinski’s introduced the term anosognosia 
he defined it as one of his examples in case in which 
the patient, though not confused, was “a little 
overexcited,” and in a later paper he pre-
sented a case in which there was “a certain 
agitation, which expresses itself by exagger-
ated loquacity, decrease in attention, and a 
tendency to erotic ideas.” Weinstein and 
Kahn noted that euphoria was common in 
patients with anosognosia. Moreover, al-
though Cutting emphasised that apathy is the 
mood more usually associated with anosognosia, 10% of his patients with ano-
sognosia were described as having euphoric mood.” 

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

Another possibility is that these syndromes 
are aetiologically related. Could anosognosia 
be a manifestation of mania? Although it is 
easy to conceive how elevated mood might 
facilitate anosognosia of hemiplegia (or other 
types of anosognosia), it is difficult to explain 
the presence of denial of ownership and disliking of the left arm (other anosognosic 
phenomena) on the basis of euphoria. 

Moreover, Starkstein et al., finding that simi-
lar frequencies and severities of major and 
minor depression were present in patients 
with and without anosognosia, suggest that 
a particular mood state may not necessarily 
influence anosognosia.

Several explanations have been proposed to 
explain the phenomenon of anosognosia. All 
The models invoke dysfunction of the cer-
bral cortex, especially the parietal areas. It is interesting that in this case functional MRI 
faulted to demonstrate decreased CBV in the 
parietal lobe.

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

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Epileptic cardiac asystole

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

Cardiac arrhythmias subsequent to epilep-
tic seizures have been recognised for more 
than 90 years. They provoke diagnostic 
difficulty and may be a mechanism of 
sudden unexplained death in epilepsy. 
Whereas sinus tachycardia was noted to 
accompanied 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 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.
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 disorientated 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. Of the episode his four hour 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 frequent in origin and therefore before 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 frontocentrotemporal region during sleep. The onset of the episode was not witnessed and the patient was found lying on the floor, regaining consciousness at about 07:06. The event EEG showed a short run of bilateral semisynchronous 2–3 Hz activity at 07:04:34 (figure A), persisting for 8 seconds before being obscured by muscle and movement artefact. Twenty four seconds later, abrupt changes in heart rate, (both acceleration and deceleration) occurring towards the end of the period of EEG abnormality. Interictally, patients with epilepsy seem no more likely than age and sex matched healthy subjects to experience arrhythmias although in one study patients with epilepsy had a faster ventricular rate and a longer QT interval than control subjects.

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

Recurrent episodes of loss of consciousness are a common clinical problem. An accurate diagnosis relies principally on the patient's and witnesses' accounts of events. Further investigations are frequently required which are often normal unless an episode is captured during monitoring. Recording solely the EEG or the ECG may result in erroneous conclusions being drawn and insufficient or inappropriate therapy being instituted.

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

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant disorder, the molecular basis of which is a 1.5 Mb deletion in chromosome 17p11.2 including the peripheral myelin protein-22 (PMP-22) gene. HNPP typically presents recurrent pressure palsies of peripheral nerves, such as the axillary, median, radial, ulnar, or peroneal nerves, at common entrapment sites.

Respiratory muscle weakness has not been previously reported in HNPP. We describe a patient with HNPP with respiratory failure and proximal muscle weakness who presented with a comatose state due to CO, narco-

The patient started to have dypsnea on exertion at the age of 44. At the age of 47, he noticed a slowly progressive weakness of the pelvic girdle and lower limbs. At the age of 57, he experienced difficulty in going up stairs. However, he was almost independent in daily life. At the age of 60, he was admitted to the Narita Red Cross Hospital with a diagnosis of myasthenia gravis. His respiratory condition in the daytime improved to that previously. However, he needed mechanical ventilation during sleep because of nocturnal hypoventilation.

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

In a neurological examination, the patient's mental state and cranial nerves were normal. Evidence of muscular atrophy was not noted. Both the lung field were normal. His respiratory condition in the daytime was normal. His vital capacity was 1.9 l (55% of the normal mean) in the sitting position, but 1.3 l (38%) in the supine position. The percentage of forced expiratory volume in 1 second was normal (99%). The thorax showed no visible hypostasis in all limbs. The patient's sensations of touch and pain were mild impaired in the four limbs (two of which were lost in the distal limbs). Sensations were diminished but not abolished in the four limbs. The patient was able to perceive light touch in all the four limbs. Sensation of vibration was normal in all the four limbs. He was able to perceive pain and temperature stimuli in all the four limbs. The patient was able to perceive two point discrimination as well as light touch in all the four limbs. There was no sensory deficit in the periphery of both hands.

A VXI permanent pacemaker was inserted. The phenytoin was withdrawn and replaced by lamotrigine. Carbamazepine was left.

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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 abnormal thin axonal myelin sheaths. The density of myelinated fibres was reduced (5726/mm2). A gene analysis disclosed a 53% gene dose of PMP-22 related to normal controls, using Southern blots of DNA digested with EcoRI. Given the possibility of superimposing demyelinating neuropathy, especially chronic inflammatory demyelinating polyneuropathy, oral prednisolone (60 mg/day) was given for 1 month. However, the patient’s clinical condition did not respond to this treatment. Pulmonary dysfunction and proximal muscle weakness were almost steady during the next 3 years.

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

Our patient recalled experiencing recurrent episodes of 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 hyperventilation 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
Ischaemic stroke in a sportsman who consumed MaHuang extract and creatine monohydrate for body building

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

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

The patient had no vascular risk factors, in particular no tobacco use, and he was perfectly fit until his stroke. He was a sportsman with 2 hours daily intensive training for body building. He was working as a baggage handler in an international airline company. During a recent journey to Miami, Florida, he bought tablets of "energy pills" in a shopping mall to enhance his athletic performances. The first drug contained MaHuang extract (corresponding to 20 mg ephedra alkaloids), 200 mg caffeine, 100 mg L-carnitine, and 200 mg creatine per capsule. The second drug contained 6000 mg creatine monohydrate, 1000 mg taurine, 100 mg inosine, and 5 mg coenzyme Q10 per scoop. He consumed 40–60 mg ephedra alkaloids, 400–600 mg caffeine, and 6000 mg creatine monohydrate daily for about 6 weeks before his stroke.

Although a paradoxical embolism through a patent foramen ovale in this patient cannot be ruled out as he recently underwent a transatlantic air flight, there was no deep venous thrombosis and D-dimers were normal. However, ephedrine has an indirect sympathomimetic effect which may mask the vasoconstrictor effect for arteriolar vasoconstriction in addition to other catecholaminergic effects. Both ischaemic and haemorrhagic stroke associated with ephedrine use have been reported.1,2 Acute myocardial infarction and acute psychosis have also been reported after taking ephedrine and other sympathomimetic drugs.3 Ephedrine and its metabolites are natural products that are used in non-prescription medicines for multiple uses. In the present case, which contains ephedrine, is used among young sportsmen and sportswomen as an energy supplement in non-prescription tablets in some countries.

Although no cardiac side effects have been reported with the use of creatine monohydrate, this compound, used in association with other drugs as energy supplement may have deleterious side effects. This may be particularly true when used at high doses in combination with sympathomimetic drugs as in our patient. Renal dysfunction has also been reported after oral creatine supplements. Our patient had a slight increase in creatinine concentration although...
it remained in the normal range. Whether the use of high doses of caffeine can enhance the cardiovascular effect of ephedrine remains a possibility as stroke after taking a combination of caffeine and amphetamine has been reported.

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 dysesthesia of the upper quadrant of her face for 1 year. In addition she had intermittent ipsilateral headache. A left sided facial palsy and hypogeusia developed. When progressive hearing loss and persistent ipsilateral tinnitus occurred she sought medical advice. She was referred to our department for further treatment after a large tumour in the left cerebellopontine angle had been demonstrated by MRI. On admission, the left corneal reflex was absent. There was marked hypoaesthesia of the first two divisions of the left trigeminal nerve and a mild left facial palsy. There was also hypogeusia of the left half of the tongue. Speech was slightly dysarthric. During examination dystonic and choreic movements of the left facial muscles were seen. The dystonic grimacing increased when the patient was being observed. There were also intermittent jerky dystonic head movements with turning of the head to the left, associated with slight elevation of the left shoulder. The facial movement disorder was clearly different from hemifacial spasm. There were no tonic or clonic synchronous contractions of facial muscles and no signs of involuntary coactivation. The patient barely noted the dyskinesias. Audiometry showed a hearing threshold at 30 Db on the left side and lack of stapedius reflex on the left side. Oculovestibular response to caloric stimulation was normal.

(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 brainstem.
decreased on the left side. Furthermore, there was mild left dysarthrochokinesia.

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

The postoperative improvement of the dystonic and choreic grimacing and the cerebral dystonia indicates a causal association between the petroclival meningioma and the segmental hyperkinetic movement disorders. Such a relation is supported also by the absence of a familiary 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. Asymmetrical blepharospasm was recently found in a patient with an ipsilateral mesencephalic cyst. Hemifacial spasm was seen in patients with demyelinating neurinomas, meningiomas, and epidermoid tumours of the cerebellopontine angle. Acoustic neurinomas and anaplastic pontocerebellar glioma can be associated with facial myokymia and spastic parietic facial contracture. Also, cervical dystonia due to tumours of the cerebellopontine angle have been reported recently.

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

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

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Acute multifocal cerebral white matter lesions during transfer factor therapy

Transfer factor is an active substance of unknown structure present in dialysable leucocyte extract which is assumed to transfer cell mediated immunity in an antigen specific fashion. The mechanisms of action of transfer factor are still far from clear; in vitro dialysable leucocyte extract increases macrophage activation and interleukin (IL) 1 production and enhances leucocyte chemotaxis and natural killer function. Transfer factor has been reported to stimulate the cell mediated antigen specific response in patients with various infections; therefore, treatment with transfer factor has been suggested in patients with selective deficits in cell mediated immunity such as in some refractory neoplasms and chronic infections. Moreover, it has been used in the treatment of uveitis. Administration of dialysable leucocyte extract has seemed to be free of hypersensitivity, long lasting side effects, or complications, except for transitory hyperpyrexia.

We report on a patient in whom multiple cerebal white matter lesions developed after taking dialysable leucocyte extract orally for uveitis. A 28 year old man was admitted to our hospital because of headache, mental confusion, and right hemiparesis. He had had recurrent bilateral uveitis from the age of 12 to 14 with resolution 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 generalised weakness after the second dose and the referring symptoms developed after the third dose.

Neurological examination on admission showed mental confusion and severe right spastic hemiparesis with Babinski's sign. No fever or meningismus were present.

Laboratory examinations on admission showed a slight increase in total serum protein (8.4 g/l, normal 6.0-8.0 g/l), although the serum protein fraction was normal, antistreptolysin tities (355 UI/ml, normal <200 UI/ml), and anticardiolipin IgG (30 UI/ml, normal 4-12 UI/ml). Negative results were obtained for HIV and hepatitis virus B and C infection were 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 asymmetric lesions in the subcortical and periventricular cerebral white matter, some of which exerted a mass effect on the nearby CSF spaces. All lesions exhibited thick ring-like enhancement after intravenous contrast administration (figure). The brain stem, cerebellum, and cervical spinal cord were spared.

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

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

The occurrence at different time of focal cerebral white matter lesions highly supports the diagnosis of multiple sclerosis, but some clinical and laboratory findings in the our patient are not typical for this condition. Mental confusion is not common at the onset and 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 cell mediated immunological mechanism. This view is further supported by recent data that show an association between non-bacterial meningitis, vaccinations, and multiple sclerosis.

Although the hypothesis that dialysable leucocyte extract had triggered an autoimmune disorder in our patient cannot be proved, our finding is in line with the report of multiple cerebral lesions after therapy with IL-2 in patients with malignancies or HIV infections.

On the other hand, the fact that acute disseminated encephalitis is often correlated with the administration of foreign proteins, such as during vaccinations or viral infections led us to postulate in this patient a cell mediated immunological mechanism. Therefore, an immunological cross reaction between viral antigens (or other foreign material contained in vaccines) and various parts of the nervous system resulting in acute disseminated encephalitis might have occurred. As already noted, dialysable leucocyte extract contains a multitude of immunostimulating or potentially activating substances so it is impossible to pinpoint which one could have been responsible for the demyelinating effect seen in our patient. This notwithstanding, our finding indicates that neurological surveillance is worthy in patients assuming dialysable leucocyte extract therapy.

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

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

According to medical history, the patient’s mother had received weekly injections of Depopovera during pregnancy. A single child born after a normal term delivery, he underwent surgery for an inguinal hernia at 3 weeks. Developmental milestones were only moderately delayed. At 9 months, he rolled instead of crawling. He walked at 15 months, spoke at 2 years with poor articulation, and still speaks in short, unelaborated sentences. His social and language development lagged 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 impression of fine finger movements, dysgraphaesthesia on sensory testing, and a manieristic gripping handshake. There were no extrapyramidal movements, extrapyramidal 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.

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Neurological examination showed bilateral hyperreflexia, mild impression of fine finger movements, dysgraphaesthesia on sensory testing, and a manieristic gripping handshake. There were no extrapyramidal

Brain CT, axial section: dense calcific deposits in the basal ganglia, thalamus, and orbitofrontal cortex consistent with Fahr’s disease.
sions. His IQ score was in the low range (Wechsler C=85 at the age of 13; Barbeau Piper=82 at the age of 17). He also presented an impairment on the Tower of London test, which measures executive function, and in a task assessing the understanding of others. These two findings are reliably present in pervasive developmental disorders, in this IQ range. In addition, his performance on the Tower of Toronto test disclosed impaired performance in procedural learning. Psychiatric assessment showed scores above the cut off for autism according to the autism diagnostic interview (ADI), a standardised interview that requires specific training and those administering it to have a 0.90 reliability with other researchers. The subject was positive for the diagnosis of autism, being above cut off values in the three relevant areas of communication, social interactions, restricted interests, and repetitive behaviours. Nevertheless, he did not present delay in language acquisition or morphological atypicalities in language development, which corresponds to DSM-IV criteria for Asperger’s syndrome.

Brain CT showed dense calcium deposits in the basal ganglia, thalamus, cerebellar dentate nucleus, and orbitofrontal cortex, consistent with Fahr’s disease (figure). SPECT showed increased activity in the basal ganglia relative to the cerebral cortex. A fine banded karyotype was normal. Serum calcium was 1.55 mM (normal 2.15–2.55 mM), phosphate 1.69 mM (normal 0.70–1.34 mM), total serum calcium was 0.80 mM at pH 7.4 (normal 1.19–1.34 mM); urinary calcium was 0.8 mM (normal 2.5–6.3 mM). Serum parathyroid hormone was below 0.6 (normal 1.0–6.55 µM), and a nuclear scan of the parathyroid glands showed an absence of activity. With a combination of vitamin D3-calcium supplementation and cognitive-behavioural therapy, serum calcium, and phosphate concentrations normalised and his behaviour improved marginally.

Asperger’s syndrome is a subtype of pervasive developmental disorder of unknown aetiology. Evidence for involvement of specific brain regions in pervasive developmental disorders is scarce and inconclusive. Although the tempo-orbital region is the most often involved in pervasive developmental disorders, abnormal functioning of the frontal lobes is suspected from replicated findings of executive function deficits and from occasional findings of frontal hypometabolism or abnormal macroscopic brain morphology. Abnormal cell counts and morphology in the cerebellar hemispheres have also been reported, but the relation of these findings to autism is controversial. Fahr’s disease consists of symmetric calcifications, located mainly in the basal forebrain and cerebellum, which are of various aetiologies. Cognitive and behavioural abnormalities may be present when calcifications occur early in development. A fortuitous association between pervasive developmental disorders and paracalcemia, given the paucity of published cases, is plausible in the present patient. Nevertheless, our case suggests that abnormal phospho-calcium metabolism could produce an autistic syndrome when brain calcifications cause specific neuropsychological deficits, due to their localisation. For example, errors of social judgement may be related to calcifications of the orbitofrontal cortex, whereas dysfunction of frontal-basal ganglia circuits may contribute to repetitive and ritualistic activities. Additionally, developmental lesions of the basal ganglia and cerebellum may contribute to the abnormalities of sensory attention, procedural learning, and motor intention in this patient.

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

Preoperative sagittal T1 weighted MRI of the cervical spine with gadolinium enhancement. A retro-odontoid and extradural mass displacing the spinal cord is seen at the craniovertebral junction.

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

The craniovertebral junction can be affected by several pseudotumorous masses extradurally located, such as rheumatoid panus, hypertrophic non-union of odontoid fracture, post-traumatic cicatrix, syringomyelia, tumorous calcium pyrophosphate dihydrate crystal deposition, tophaceous gout, calcification of the posterior longitudinal ligament, synovial chondromatosis, and hypertrophy of the ligamentum flavum. Hypertrophy of the atlantoaxial ligaments as a consequence of degenerative disease was recently recognised as an individual entity. Only five previous cases have been published. 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 osteoarthritis or instability on plain cervical radiography and CT. A bone scan with ⁹⁹Tc was unremarkable. Magnetic resonance imaging showed a retro-odontoid extradural mass that was homogeneous and isointense on T1 weighted signal, demarca-

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

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

Brain CT on admission showed a discrete and linear high density at the left ambient cistern without other intracranial lesions. On the next day CT showed an obscure low density lesion at the dorsolateral midbrain in addition to the previous lesion (figure).

Brain MRI, taken 3 days later, demonstrated an intraparenchymal lesion, at the surface of the left dorsolateral midbrain in high intensity on a T2 weighted image. The high intensity lesion corresponding to haematoma on CT was seen in the ambient cistern (figure). Taking both CT scans and MRI into consideration, this case was diagnosed as traumatic midbrain contusion.

The loss of pain and temperature sensation improved gradually and the patient was discharged 2 weeks later.

T2 weighted images 1 month later showed a more localised lesion in the same area. The coronal slices showed a high intensity lesion at the level of lower midbrain coinciding with the tentorium 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 craniocebral injury. Responsible lesions for sensory impairment, detectable by neuroimaging studies, almost always accompany associated neurological deficits. To our knowledge, a selective injury at the spinothalamic or trigeminothalamic tracts due to closed head injury has not been highlighted in the neurological literature.

The MR images in our case showed a discrete lesion at the left dorsolateral midbrain. Topographical study at this lower midbrain level showed that the lateral and ventral spinothalamic and ventral trigeminothalamic tracts pass at the surface of this level by carrying a superficial somatosensory 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 from 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. 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 preconditioned with narrow tentorial incisura, which may have been the case in our patient.

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

(A) CT on admission showed a discrete and linear high density at the left ambient cistern. (B) Axial T2 weighted image taken 3 days later showed an intraparenchymal lesion, at the left posteroslateral midbrain in high intensity (arrow). The margin was rather obscure. The high and low intensity lesion corresponding to haematoma on CT was seen in the ambient cistern in the axial image (arrow head) Taking both CT scans and MRI, this case was diagnosed as traumatic midbrain contusion. (C) An axial T2 weighted image 1 month later demonstrated a more discrete lesion at the dorsolateral midbrain tegmentum (arrow). (D) A coronal image showed a discrete high intensity lesion at the level of the lower midbrain (arrow) coinciding with the level of the tentorium, which was shown in low line between the occipital lobe and cerebellar hemisphere. The distance between the tentorial margin and brain stem was shorter on the injured side.


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Toluene induced postural tremor

We read with interest the article by Miyayi et al1 and comment on the medical treatment of toluene induced tremor. Microdialysis experiments in rats have shown that inhalation of toluene increases extracellular γ-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 cerebral 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, which showed remarkable clinical and iconographic similarities with that described by Miyayi 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 of heredodegenerative disorders in which the dentatorubro-olivary system is affected. In addition, there is evidence that catecholaminergic pathways are also involved in the type of ataxias, supported by loss of brainstem uptake of these neurotransmitters in the CSF of patients with heredodegenerative ataxias. 3 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) abolished postural tremor and ataxia completely over a 3 month period.


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

Nabbout et al1 have attempted to identify the risk factors for the progression of subependymal nodules into giant cell astrocytomas (SEGAs) in the tuberous sclerosis complex. In attempting to develop screening strategies that avoid iatrogenic morbidity, patient inconvenience, and excess cost, it is essential that the natural history of these lesions in the general population of patients with tuberous sclerosis complex be understood well.

We think that there are two problems with this study that should make the physician cautious about accepting the factors identified by 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 point is that the authors have made a potentially misleading decision to exclude more than half their study sample because they do not have lesions close to the foramen of Monroe. This 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. This study selects 24 of 60 patients who had met their entry criteria but does not state how many of the excluded 36 patients had no subependymal nodules or nodules that were not “near the foramen of Monroe”. Information 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 lesions will become invasive is important. As subependymal nodules and SEGAs seem to be histologically identical it is unlikely that pathologists will provide an answer. The study of Nabbout et al tests some of the factors identified by others. However, the definitive answer will not be provided by studies of selected samples but by follow up of a population based sample of patients with tuberous sclerosis complex. In the absence of such a study we would be cautious about implementing screening programmes based on what may be misleading criteria.

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

We read with interest the article by Sasaki et al2 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 in the upper limbs and little or no effect of either a bulbar nature or in the lower limbs. Thus Hu et al3 coined the term flail arm syndrome, to describe a subgroup of patients affected by ALS that predominantly showed signs of lower motor neuron disease in the upper limbs, without significant functional involvement of other regions on clinical presentation. This subgroup of patients was clinically characterised by the display of progressive atrophy and weakness affecting the proximal muscles in the upper limb muscles in a more or less symmetric manner.

Recently, along these lines, Katz et al4 described a series of patients affected by an adult onset motor neuron disorder restricted to the upper limbs, with severe proximal and varying degrees of distal involvement, calling it amyotrophic brachial diplegia syndrome.

Other terms used to describe this form of ALS have been dangling arm syndrome, suspended form, orangutan sign, and a form of ALS have been dangling arm syndrome, suspended form, orangutan sign, dead arm sign, bifacial palsy, rimozelic amyotrophy, and the idea of naming it a distinctive phenotype of a neurogenic
“man-in-the-barrel” syndrome has even been suggested.

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

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

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

1 The prevalence of this form of ALS constituted 10% of the ALS group as a whole (p = 0.05).2 The age of onset of this form was similar to the rest of ALS. (3) There was a clear predominance among men (the male/female ratio was 9:1 in this form, compared with 1:5:1 in the total ALS group). (4) There was a higher median survival (a median survival of 57 months compared with 39 months in the ALS group).

Some of these patients have a long ALS clinical course, in that they usually preserve ambulatory ability, albeit with gait disorders, for more than 5 years after the onset of symptoms.

On a personal level, we also note two findings characteristic of these patients. In the initial stages of the illness, there (in the posterior longitudinal ligament disclosed by cervical spondylosis. In: Norris FH, Kurland L, eds. Motor neuron disease: research on amyotrophic lateral sclerosis. Tokyo: Kanehara, 1965;866–7).

As in their patients transcranial magnetic stimulation was similar to our results. However, we wonder whether cerebral cortical blood flow was preserved in their patients, because our SPECT study suggested frontal cortical hypoperfusion, particularly in the anterior opercular and medial frontonal regions. Anterior opercular lesions produce facio-pharyngo-glosso-masticatory paresis (anterior opercular syndrome), and damage to the medial frontonal regions, including the supplementary motor area, causes speech expression disorders. White matter lesions can disrupt afferent and efferent fibre connections with cerebral language areas, resulting in dysfunction of these cortices.3,4 Therefore, we postulated that isolated dysarthria results from interruption of corticousubcortical networks indispensable for speech output, 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 these ascending (and descending) pathways.5

To assess corticopontocerebellar tract function, Urban et al investigated cerebellar blood flow in patients with isolated dysarthria using HMPAO-SPECT. The study concluded that the corticopontocerebellar tract is preserved in isolated dysarthria because of no evidence for cerebellar diaschisis on SPECT. Their SPECT findings on cerebellar blood flow were similar to our results. However, we wonder whether cerebral cortical blood flow was preserved in their patients, because our SPECT study suggested frontal cortical dysfunction as an underlying mechanism of isolated dysarthria, Langston et al have shown evidence in three of seven patients reported by Urban et al and in two of 12 by us. This indicates that isolated dysarthria originates in incoordination of multiple organs necessary for speech articulation as well as language expres-

Sasaki et al reported necropsy cases in our article concerning the atypical form of amyotrophic lateral sclerosis (ALS).6

Over many years, several researchers have recognised this peculiar distribution of muscle atrophy in clinical practice. The clinical manifestations consist of the muscular atrophy confined to the shoulder girdle and the arms (proximally dominant), absence of deep tendon reflex in the arms, almost normal deep tendon reflex in the legs, and subluxation of the shoulder joints. Some patients progress to bulbar involvement. One of our patients disclosed that the corticopontocerebellar tract is preserved in isolated dysarthria because of no evidence for cerebellar diaschisis on SPECT.
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 found a reduced intracortical inhibition in a group of patients with genetically confirmed Huntington's disease. Hanajima et al suggest that the discrepancy between the two studies might be due to di 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.” They postulated that our cases, because of the reported corre-

lation 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, whereas 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 disease and may even precede the appearance of choreal diskinesias. 1 Chorea itself is often reduced in the more advanced Huntington's disease stages.2 It is unlikely, therefore, that any of the physiological 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 impairment of somatosensory evoked responses and long latency stretch reflexes in the second. 3

We were not really surprised at the results of Hanajima et al. 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; 4 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 0.3 mV in the study of Hanajima et al). This may induce a different sensitivity of the test, and the amount of intracortical inhibition in our normal controls is greater (see also 5) than in the study of Hanajima et al.

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

The authors reply: We were very grateful for the response of Abbruzzeze et al to our paper. We completely agree with their opinions.

The discrepancy between the two studies may not be mainly due to the different stage of the disease between our 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 intracortical inhibition was normal even at the same stage of the disease as that of the patients of Abbruzzeze et al, if studied with our method.

We also consider that methodological differences are very important in paired magnetic stimulation. The results strongly depend on the intensities of both a conditioning and a test stimulus. Especially, the intensity of the conditioning stimulus is critical. We have no difficulty in showing normal inhibition, but have much difficulty in showing reduced or absent inhibition because of such marked dependence of the results on the intensities of stimulation. Therefore, we used a wider range of the conditioning stimulus before we confirmed inhibition in studies of patients. 6 We used an intensity of 5% less than the active threshold as a conditioning stimulus in our magnetic stimulation study. This is the intensity of the conditioning stimulus we have used in all our experiments. We consider that this is the best way to test purely choreic inhibition because we have no direct way of detecting the threshold of the motor cortex. Our results are important because they confirm our previous results. However, we have two completely different interpretations of these results. (1) The intracortical inhibition is normal in Huntington's disease. Abbruzzeze et al showed the reduced inhibition because they used a high intensity conditioning stimulus with which the degree of the
Critical closing pressure: a valid concept?

Czosnyka et al recently published a study investigating the clinical significance of critical closing pressure (CCP) estimates in patients with head injury. We see problems both with the theoretical foundation of their CCP concept and with the interpretation of their results.

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

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

(1)

At the time of systolic and diastolic pressure amplitudes (ABP, ABPd), respectively, it follows that systolic and diastolic FVs (FVv, FVd) should be equal to (ABP−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 in general much higher than resistances determining dynamic pressure/flow relations (CVR1) as in the case of pulsatile flows. 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; AI=amplitude of the pulsatile pressure wave; F1=amplitude of the pulsatile flow wave):

\[ FV = \frac{ABP - CCP}{CVR0} \]  

(2) F1=AI × CVR1

Inserting equations 2 and 3 into the frequency domain equation for CCP2 of the authors:

\[ CCP2=ABP-A1/F1 × CVR0 \]  

(4)

leads to

\[ CCP2=ABP×CVR1/ABP−ABP×CVR0 \] =ABP×(1−CVR1/CVR0)+CVR1/ 

CVR0×CVR2

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

\[ CCP2=0.5ABP×0.5CVR0 \]  

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 FV values with mean ABP found by the authors (r=0.5; p<0.05). According to the original idea of Burton,1 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 vasoconstruction. 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 hypcapnia). In the case of ABP<CCP and a small vessel collapse according to the model of the authors, CVR should increase towards \(100\%\) 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

\[ FV = \frac{ABP−ICP}{CVR0} \]  

(6)

and equation 5 to

\[ CCP2=ABP−CVR1/CVR0 \]  

(7)

Equation 7 explains well the positive correlations found between CCP2 and ABP and between CCP2 and ICP, respectively, without assuming a connection between CCP2 and Burton’s concept of “critical closing pressure”.

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Czosnyka et al reply: We thank Diehl for the interesting letter provoking some mathematical considerations about cerebral haemodynamics. We need to emphasise that our primary intention was to investigate Burton’s hypothesis in patients with head injury of 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 Aassid proposed the mathematical formula taken for calculations:

\[ CCP1=ABP−ABPpp; \]  

ABPpp and FVpp are peak to peak amplitudes. A grapherical 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 the formula, the 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:

\[ CCP2=ABP−A1/F1 × CVR \]

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 wave form against momentary values of FV waveform knows that it never plots a straight line (as equation (1) implies). We believe that “clouds” of systolic and diastolic values of ABP and FV waveforms (fig 1 in) one can rather see an ellipsoidal shape which is very seldom regular enough to be approximated by a straight section. Therefore, equation (1) in Diehl’s letter is not correct. In fact, CVR is a frequency dependent variable (represents vascular impedance) and if a linear theory can be applied, division in (1) should be substituted by a convolution with an inverse 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 0.31) and CVR1 0.972 (SD 0.29), the difference being 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 presuming ICP was constant, CCP should decrease. A rather weak (though significant) correlation suggests that not all of our patients were pressure reactive or ICP was not always constant.

The final issue concerning negative flow velocities is a trap Diehl has prepared for himself. We never suggested that any factor interpretable as cerebrovascular resistance (CVR0 or CVR1) should be involved in the concept of critical closing pressure. From the definition, closing is a strongly non-linear phenomenon, therefore applying linear theory here is very
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thought to share a similar pathophysiology of the globus pallidum internum is induced dyskinesias in Parkinson's subthalamic nucleus and levodopa cessation.

We fully agree with the considerations regarding equations (6) and (7). CCP can be understood as a combination of ABP and ICP with coefficients describing properties of the cerebrovascular bed. Whether it simplifies our knowledge—we personally find it doubtful. Finally, we are truly obliged to Diehl for an opportunity to have this interesting discussion.

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

Reduction in the neuronal activity of the subthalamic nucleus leading to diminished excitation of the globus pallidum internum is associated with chorea-ballism in monkeys. Levodopa induced dyskinesias are currently thought to share a similar pathophysiology but recent findings also suggest that abnormal patterns of neuronal firing in the globus pallidum internum may be as relevant. Data from both parkinsonian monkeys and patients with Parkinson's disease submitted to lesion or functional blockade of the subthalamic nucleus are in keeping with such a general principle, but the threshold to induce dyskinesias in the parkinsonian state is higher than in intact animals. The case recently described by Figueiras-Mendez et al is extremely interesting as it suggests that functional inhibition of the subthalamic nucleus by high frequency stimulation blockades levodopa induced dyskinesias. This is clearly at odds with the current pathophysiological model of the basal ganglia. Thus, the finding of Figueiras-Mendez et al raises the intriguing possibility that dyskinesias depend or are mediated by neuronal firing in a given region of the subthalamic nucleus, which was blocked by high frequency stimulation. Measurement of afferent synaptic activity by the technique of 2-deoxyglucose (2-DG) uptake showed an increment in the subthalamic nucleus, which was compatible with increased inhibition from the globus pallidum externum, particularly in the ventromedial tip of the nucleus. This contrasts with the findings in monkeys with chorea induced by pharmacological blockade of the globus pallidum externum, in which 2-DG uptake was maximal in the dorsolateral portion of the subthalamic nucleus, where the sensorimotor region lies. A recent anatomical study also showed that the cortical-subthalamic nucleus con-nection is somatotopically segregated, so that fibres from the supplementary motor area project to the most medial portion and fibres from the primary and premotor areas terminate in the lateral region of the subthalamic nucleus. All this heterogeneity may have pathophysiological relevance, one aspect of which could be the findings in the patient reported by Figueiras-Mendez et al. However, before the findings of this case may be sustained, one needs to establish the role of the subthalamic nucleus in the origin of levodopa induced dyskinesias, 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 dyskinesias only relieved by reduction in levodopa intake. Moreover, Benabid et al pioneered this technique, consider the induction of dyskinesias by high frequency stimulation of the subthalamic nucleus as a good indicator of a very positive response. If, as assumed, the subthalamic nucleus in the globus pallidum internum are placed dorsocaudally to the subthalamic nucleus and could be blocked by high frequency stimulation. (3) When the recording electrode is placed in the globus pallidum internum, the activity is normal or lesser, neuronal activity is characterised by action potentials of large amplitudes (0.5–1 mV) with low background activity, tonically firing neurons, and absent sensorimotor responses (“driving”). All these characteristic features were 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. Ideally we would like to see the trajectory and length of the different recording tracks, the effects of microstimulation, and the posttreatment MRI with measurements of the location of the tip of the electrodes. If, as assumed, the subthalamic nucleus was indeed correctly targeted in this patient, the pathophysiology of the basal ganglia will need to be revisited.

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Nitrergic 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 recent editorial is the neuroprotective effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or “statins” in cerebral ischaemia. Preliminary studies have shown that statins modulate brain nitrergic synthesis and NO activity in a neuroprotective manner. Data from a murine model of ischaemic stroke demonstrate that prophylactic statin therapy reduces infarct size by about 30%, and improves neurological outcome in normocholesterolaemic animals.2 In this investigation, statin therapy directly upregulated endothelial NO synthase in the brain without altering expression of neuronal NO synthase. Recent findings also suggest that statin therapy influences the transcription of inducible NOS. Lovastatin has been shown to inhibit cytokine mediated upregulation of inducible NO synthase and production of NO in rat astrocytes and macrophages, and this inhibition may represent a novel means of suppressing inflammatory responses that accompany ischaemia. Most interestingly, these preliminary findings suggest that statin therapy may modify the friendly and unfriendly faces of brain NO in a synergistically neuroprotective manner. These and other vascular effects of statins in cerebral ischaemia are potentially of great importance in human neuroprotection and ongoing clinical trials of the The PROSPECTIVE Study of Pravastatin in the Elderly at Risk (PROSPER) study will help clarify their role in human cerebrovascular disease.

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O'Mahony replies:
The comments of Vaughan and Delanty draw attention to the act of narrating which may detract from realistic illusion, so reducing the emotional intensity of what is being represented. It is a device much favoured by postmodern writers, who expose the nature of the 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 immune responses in the nervous system. There follows a chapter that integrates the neurobiology of multiple sclerosis with contemporary issues of autoimmunity, cell injury, and repair. Next, a chapter on inflammatory demyelinating diseases and 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 concludes with chapters on para-neoplastic disorders of the CNS, stiff man syndrome, neurological complications of the wide variety of pharmacological agents that may have favourable effects on endothelial NOS as stroke preventive therapy. Rather, it is focused on the possible ways of inhibiting neuronal NOS and inducible NOS mediated nitric oxide release after the event of acute stroke. At present, there are no clinical studies indicating that acute administration of statins in animal models of ischaemic stroke is neuroprotective. Their point about statins and endothelial NOS is interesting, but not relevant to neuroprotective therapy in acute stroke.

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

Covering all aspects of Alzheimer’s disease research from the correct diagnosis to basic science approaches of treatment is ambitious to the neurologist without much experience of the field, predominantly based in Europe. The peripheral nerve and plexus okay to the neurologist without much experience of the field, predominantly based in Europe.

CLARE GALTON

Alasdar Coles


Organ transplantation, once medical exotica, is now almost routine. In the United Kingdom each year are performed cadaveric organ transplants of about 1800 kidneys (in addition to 160 live kidney donors), 700 livers, and 450 heart/lungs (UK Transplant Support Service). In basic surgical techniques were established at the beginning of the century in canine models. Transplantation of these experiments to humans awaited safe and effective immunosuppression. Until the 1960s, the only forms of immunosuppression were radiation (total body or total lymphoid) and non-selective chemical reagents (benzene and toluene). Then the antiproliferative drug 6-mercaptopurine (6-MP), introduced, shortly followed by a derivative, azathioprine, with improved oral bioavailability. Combined with corticosteroids, these allowed the first human solid organ transplants to be performed: in 1963 the first lung transplant in Mississippi and liver transplant in Colorado. Then in 1967 Christian Barnard captured the world’s imagination with the first heart transplant. His technique has been modified slightly since, but his achieving success of organ transplantation rests mainly on improved immunosuppression with drugs that selectively suppress lymphocytes by inhibiting lymphokine generation (cyclosporin A, tacrolimus), renal transduction (sirolimus, leflunomide), or differentiation (15-deoxyspergualin) pathways. As a result, over the last 10 years in the United Kingdom, the 1 year survival of grafts has improved from 80% to 90% (kidney), 55% to 75% (liver), and 70% to 90% (heart/lung).

Wijdicks estimates that 10% of transplantation patients have a significant neurological complication, the etiology of which being neurotoxicity of immunosuppressive drugs, seizures, and failure to awaken. Yet this is the first text devoted to the neurological aspects of organ transplantation. It is therefore a timely subject for another title in the excellent Blue Books Of Practical Neurological series. Twenty authors contribute (one Dutch, one Swiss, the rest American) to four chapters on the transplant procedures themselves followed by 10 chapters on neurological complications of transplantation including failure to awaken, and psychiatric, neuromuscular and demyelinating complications. Especially useful to the neurologist without much experience of transplantation are the comprehensive chapters on immunosuppressive drugs and the opportunistic infections associated with them (most commonly Listeria monocytogenes, Aspergillus fumigatus, and Cryptococcus neoformans). The peripheral nerve and plexus injuries associated with transplantation are painstakingly described; astonishingly a significant ulnar neuropathy occurs in up to 40% of kidney transplants in the Cincinnati Transplant Tumour Registry has recorded information on 10 813 cancers arising de novo in organ allograft recipients worldwide and here are presented the data in the 300 of these with CNS involvement. This is one for the shelves of any neurologist involved in organ transplantation.

CLARE GALTON

Alasdar Coles


Volume nine of the Current Issues in Neurodegenerative Disease series examines the interplay between cerebrovascular disease and dementia, particularly Alzheimer’s disease. Two hundred pages of what are essentially 20 brief review articles comprise this text, sadly without any illustrations. But 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 dementias, the arguments for a pure vascular dementia, the role of Alzheimer’s disease in the genesis of demen- tia after stroke, the complications which seem to cross paths more often than would be expected by chance alone, and more often than can be explained by the presence of unusual angiopathy and recurrent lobar haemorrhages. Perhaps common genetic factors are responsible here and 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 neu- rologists, although it will no doubt be a source of reference to those working in the field of cognitive disorders, particularly vascular dementias.

Peter Martin


Evolutionary biologists would probably tell us that the enchantment of stories is due to survival having been dependent on the passing of oral culture from one generation to the next. Information put in narrative form not only delights, but is easily recalled. Storytelling also constructs the interactive observing, 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 see the awareness and use of narrative in clinical practice as a construct that can both
deliver effective care as well as act as a conceptual bridge between the different disciplines. One of the great pleasures of being a doctor has always been listening to patient’s stories, but the editors of this book fear that this essential art can be overtaken by dull scientific pragmatism. But in the most outstanding chapter, writes a lucid and well reasoned account of the need to search for and maintain narrative meaning in treating psychosis. This avoids the dehumanising effect to both patients and professionals of identifying individuals by their illness as in schizophrenics. Every psychiatric library should buy this book for this paper alone, which should be required reading for all psychiatric trainees.

The rest of this book is of variable quality. There is a rather prosaic essay on gender and psychiatric training. The concept of the need to search for and maintain the clinical narrative orientation will clearly be of particular interest to those who treat children and their families. The chapters on infantile spasms and Lennox-Gastaut syndrome are informative and provide some new but speculative insights into the pathogenesis of spasms. However, it was surprising that severe myoclonic epilepsy of infantile type did not merit a specific chapter in view of the unique electroclinical evolution and natural history of this syndrome. The crucial issue of the cognitive and behavioural sequelae of early and frequent seizures on the immature brain, which is probably of most concern to both clinicians and families, is succinctly addressed in two chapters—although a clear and consistent cause and effect relation remains to be established. The chapters covering basic neurophysiology, neurochemistry, and neuropathology, are erudite and fascinating but at times are barely comprehensible.

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. Two excellent 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 for 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, but I would recommend because some aspects of the practical management of violence are missing—for example, a documented risk-benefit analysis, good failsafe communication, or deciding when to detain. One of the last chapters is a very good account of the management of hyperactivity in childhood, with good practical advice on the use of methylphenidate.

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

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 great erudition, but provides a useful list of references.

There are a few cavils. The section on treatment of anxiety is skimpy (one and a half pages) compared with the treatment of affective illness (22 pages) or schizophrenia (59 pages). The brevity is only partly explained by the undeveloped state of that particular area of psychopharmacology. Sections on common indications to cold 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