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.1 Surface EEG is either normal or showing non-specific slow waves.3 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 ganglia. As hyperperfusion in ictal cerebral SPECT is closely linked to epileptic activities,4 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 Antiepileptic drugs were withdrawn to facilitate seizure recording.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 hyperfusion area over the left hemisphere. Interictal surface EEG was non-lateralising but ictal EEG disclosed a right hemispheric onset. On withdrawal of antiepileptic drugs, seven complex partial seizures with secondary generalised tonic clonic seizures were recorded within a period of 72 hours. His usual antiepileptic drugs were then restarted. Thirty hours after his last secondary generalised tonic-clonic seizure, he began to develop emotional lability, talking nonsense, restlessness, auditory hallucination, persecutory delusion, and delusion of superstition. Cerebral SPECT study, performed 2 days later while his psychotic features persisted, showed two relative hyperperfused areas over the right temporal neocortex and contralateral basal ganglion in addition to the original hypoperfused area over the left hemisphere. An antipsychotic agent (thioridazine) was
started after the cerebral SPECT. His psychotic symptoms resolved 2 weeks later with full recovery.

Cerebral SPECT performed during the interictal period (IP) and during postictal psychosis (PP) were analysed visually and areas of hypofunction were identified. Quantitative data at interest of regions (ROIs) were measured on coronal and axial slides containing basal ganglia (BG), mesial (MT), and lateral (LT) temporal lobe structures. Asymmetry index (ASI) was calculated as \((\text{ROI focus−ROI contralateral}/\text{ROI focus})\times100\). We set an arbitrary change of ASI >100% to be significant. As there were only two patients, statistical testing was not performed.

Both patients showed postictal psychosis and had a regional increase in rCBF over the right temporal neocortex and the left basal ganglia compared to their interictal study (figure). Quantitative analysis for patient 1 showed changes of ASI during IP and PP over right MT was +75% (-6.4647 to -1.65289); over the right LT was +1167.8% (1.07927 to 12.55764); and over the left BG was +206.8% (-2.07373 to 2.21574). Quantitative analysis for patient 2 showed changes of ASI during IP and PP over right MT was -3.8% (13.14217 to 12.64158); over right LT was +178.6% (10.4696 to 18.70057); and over left BG was +155.9% (5.85556 to 3.27522).

Postictal psychosis is a distinct clinical event associated with temporal lobe epilepsy.\(^1\) The diagnosis of postictal psychosis requires a close temporal relation between bouts of complex partial seizures and the onset of psychosis. The psychosis usually develops after a cluster of complex partial seizures and the onset of psychosis is usually benign and predictable.\(^2\) In our patients, the duration of psychotic disturbances lasted from 1 to 14 days, which is in keeping with the good prognosis. Antipsychotic drugs, such as haloperidol and fluphenazin are usually prescribed.\(^3\)

The underlying mechanism of postictal psychosis is unknown. Postictal cerebral hypofunction has been postulated as an analogy to Todd’s paralysis after seizure.\(^4\) 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.\(^5\)

To conclude, our results are contradictory to the hyperfusion 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.

<table>
<thead>
<tr>
<th>Anti-FN mAbs(^6)</th>
<th>Anti-TN Ab fragments(^1)</th>
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<tr>
<td>IST-4</td>
<td>IST-9</td>
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<td>Recognised isoforms</td>
<td>Total FN</td>
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<td>Distribution of the isoform (s)</td>
<td>Widespread</td>
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Characterisation of the employed Abs and distribution of the recognized isoforms.
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 neighbouring AVMs.

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

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

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Hashimoto’s encephalopathy presenting as “myxoedematous madness”

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

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

A 63 year old market stallholder without medical or psychiatric history was brought to a local psychiatric hospital by the police. His business had been in decline for several months, and his family had noticed uncharacteristic emotional liability. In the weeks preceding admission he had experienced delusions and hallucinations, and exhibited delusional, uncharacteristic behaviour. He had reported a vision of the crucifixion, and hearing the voice of his dead mother. He claimed that his voice was that 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 subsequently referred him to a neurologist. He described 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 neuropsychological deficits coupled with the profound global disturbance of cognition. The psychiatric component of his illness recovered fully, and the antithyroid microsomal antibody titre fell markedly after thyroxine replacement, although his mild neuropsychological deficits remained unchanged. Corticosteroids were not used at any stage.

The response to thyroxine does not, in itself, imply that the cerebral illness had an endocrine origin; a recent report described a patient with CJD who presented with an alien hand sign. We suggest that CJD should be included in the differential diagnosis of diseases which present with an alien hand.

Creutzfeldt-Jakob disease, one of the human prion diseases, is characterised by rapidly progressive mental and motor deterioration.1 Voluntary movements occur in above 90% of the patients in the course of the disease, the most common being myoclonus, parkinsonism, hemiballism, and dystonia. We report on a patient with CJD who manifested the alien hand sign. We suggest that CJD should be included in the differential diagnosis of diseases which present with an alien hand.
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 conversation, haematology, and sedimentation rate were normal. No grasping of either hand or foot was present. The patient denied that they were voluntary. No grasping of either hand or foot was present. He was unaware of either hand or foot was found. The patient had no cortical sensory loss.

The laboratory data including blood chemistry, haematology, and sedimentation rate were normal, as were folic acid, vitamin B₆ concentrations, and thyroid function. Venereal disease research laboratory and HIV tests were negative. The cerebrospinal fluid had normal content. Brain CT showed mild cerebral atrophy. An EEG showed a diffuse slowing at admission. Within a week, repeated EEGs showed triphasic waves with a periodic pattern of 1-1.5 Hz.

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

This short fatal neurological disease manifested by fulminant dementia, myoclonic jerks, and extrapyramidal and cerebellar dysfunction was strongly suggestive of CJD. The periodic EEG pattern reinforced this diagnosis. Our patient’s alien hand was part of the otherwise characteristic clinical picture of CJD, but occurred early in the course when no myoclonic jerks were present. We are aware of only one report of alien hand in CJD. MacGowan et al. described two patients with CJD and a myoclonic alien hand syndrome. In one patient the left arm “was noted to have spontaneous movements which appeared purposeful...wandered out of her view”. In the second, the alien limb involuntarily raised and performed semi-purposeful movements.

One common denominator between CJD, corticobasal degeneration, and progressive multifocal leuкоencephalopathy, in which an alien hand sign has also been described, is multifocality. In corticobasal degeneration, it was proposed that more than one site is affected or that a “release” phenomenon occurs accounting for the aetiology of alien hand.

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

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Recurrent peripheral neuropathy in a girl with celiac disease

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

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

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

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

Laboratory investigations showed a white cell count of 9300/mm³. The results of the following investigations were within the normal limits: haemogram, erythrocyte sedimentation rate, serum urea, nitrogen, electrolytes, creatinine, glucose, transaminase, bilirubin, immunoglobulins (Igs), lead, iron, copper, urinalysis, urinary porphyrin, folic acid, and vitamins A, B₆, B₁₂, and E. Antibodies to Campylobacter jejuni, Yersinia enterocolitica, antinuclear antibodies, specific and non-specific organ autoantibodies, IgA and IgG antinuclear antibodies (ANA), IgG antineutrophil cytoplasmic antibodies (ANCA), and IgA antireticulin antibodies (ARA), assessed by enzyme linked immunosorbent assay (ELISA) and immunofluorescence (IF) were also negative. Lumbar puncture was not performed. Anti-bodies against gangliosides GM1 and GQ1b, myelin associated glycoprotein and myelin...
basic protein were not tested. Nerve conduc-
tion studies were consistent with a predomi-
nately motor demyelinating peripheral neu-
ropathy (table). Her symptoms improved
suddenly 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 in-
cluding burning parasthesiae. On neurologi-
cal examination the legs showed marked diminu-
tion in muscle power; absent deep tendo-
ner 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 were assayed
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,
reviewed 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,
in fact, neurological complications of celiac
disease are rarely encountered and are mostly
confined to the CNS: to the best of our
knowledge, there are only two previously
reported cases of PNS involvement in children
with celiac disease. In both cases, however,
these were chronic axonal polyneuropathies
presenting during a gluten free diet.¹

In both episodes in the present case neuro-
physiology was strongly supportive of a
demyelinating peripheral neuropathy, which is
most commonly attributed to a direct
immune mediated attack to the myelin.

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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” cere-
brovascular disease suggests that neurologi-
cal signs indicative of generalised organic
brain damage may occur in the absence of
completed stroke.¹ These soft signs include
primitive reflexes (frontal release signs), rep-
resenting an anatomical and functional deaffer-
mentation of cortical from subcortical struc-
tures. Primitive reflexes are known to occur in
a wide variety of dementias, including
Alzheimer’s disease² and vascular dementia.³

It is likely that the presence of undetected
cerebrovascular disease accompanying 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
vascular disease found that 72 of the
144 patients who had not experienced a
temporary ischaemic attack or stroke were
found to have a degree of carotid stenosis of
between 60% and 99%.⁴

In the present study, the prevalence of
primitive reflexes was examined in a sample of
people with peripheral vascular disease and a
non-vascular control group. Independent
predictors of these reflexes were also 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 and a period of inpatient
rehabilitation. All participants were aged 65
and over at the time of interview. Patients
with peripheral vascular disease had all clini-
cal and Doppler proved evidence of periph-
eral ischaemia. Controls were interviewed
between 6 months and 1 year after their
operation. Both groups had no history of
stroke or transient ischaemic attack.

A more detailed description of instruments
is provided elsewhere.⁵ All subjects were
examine 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 palmpomental, 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, wish to die, and suicidal ideation within the past year were also recorded, as were blood pressure and a checklist for chronic physical illness.

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

Patients with peripheral vascular disease had a higher mean score on the frontal release signs scale than controls (5.8  (SD 4.6) v.s 1.7 (SD 1.0)) (Mann-Whitney U=1,000, Z=-3.33, two tailed p=0.001), as well as on glabellar and rooting reflexes (table). Only one variable (trailmaking B test time) was entered into the equation; this accounted for 23% of the variance in FRSS score (B=4.6, 95% confidence interval (95% CI) (B 1.3–8.0, p=0.01).

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

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

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<tr>
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<th>Hand grasp</th>
<th>Foot grasp</th>
<th>Glabellar</th>
<th>Palpomental</th>
<th>Paratonia</th>
<th>Rooting</th>
<th>Snout</th>
<th>Sucking (tactile)</th>
<th>Sucking (visual)</th>
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*Higher mean score in people with peripheral vascular disease.
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. 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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appropriately. Neurological examination showed contralateral gaze preference, supra- 
nuclear vertical gaze palsy, difficulty converging, left sided flaccid hemiparesis, and dense, left sided hemianesthesia. Deep tendon reflexes were absent on the left and Babinski's reflex was present on the left. In addition, visual extinction and neglect were present. At the time of onset of right sided weakness the patient insisted that he was “fine,” and an ambulance was called over his objections. After being examined, the patient acknowledged that he had had a stroke, but, despite his hemiparesis, insisted that he was ready to go home and go back to work. His belief in his ability to walk led to near falls, and he was made more precarious to the nurses’ attention for closer observation. He told the nurses that someone else’s arm was in his bed. On one occasion, holding up his left arm with his right, he told the nurse to “take it away; it keeps scratching me.” That the left arm “smelled funny” was another reason he wanted the nurses to take it away.

Four weeks after the stroke he first acknowledged that his left arm belonged to him. However, he was consequently recalled being otherwise. By this time he had a moderate hemiplegia and recognized “a little weakness,” but continued to insist that he was well and able to return to work. By the 6th week and the patient more consistently acknowledged that he was weak on the left side of his body. A request for disabled housing “so that I won’t be a burden to my family“ seemed to indicate an appreciation of his impairment, since he was still working within an hour of making such statements the patient might insist that after a week’s exercise he would be ready to return to work. His awareness of his hemiplegia fluctuated for 8 weeks, with occasional strokes being fixed, but remaining shallow after 12 weeks; he no longer planned to return to work and applied for social security disability insurance “because they say I’m disabled.”

The patient’s mood was remarkably cheerful and optimistic. A week after the stroke he was noted to praise extravagantly the hospital and boasted of having fathered 64 children. 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 used it as one of his examples. In case in which, though not confused, was “a little overexcited,” and in a later paper he presented a case in which there was “a certain agitation, which expresses itself by exaggerated logorrhea, a decrease in attention, and a tendency to erotic ideas.”

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

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**Epileptic cardiac asystole**
A patient was 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 electrographic seizures. After changes to antiepileptic medication and the insertion of a permanent cardiac pacemaker he has had no further episodes. In cases of epileptic cardiac dysrhythmia, isolated ECG or EEG records may prove insufficient and prolonged simultaneous EEG/ECG monitoring may be required.

**Cardiac arrhythmias subsequent to epileptic seizures** have been recognised for more than 80 years. They provoke diagnostic confusion and may be a mechanism of sudden unexplained death in epilepsy. Whereas sinus tachycardia was noted to accompany more than 90% of epileptic seizures, isolated bradycardia was seen much
less commonly (only 1 of 74 seizures recorded). A review in 1996 of the “ictal bradycardia syndrome” showed only 15 documented cases in the literature of either bradycardia or asystole associated with seizures. Most patients had temporal lobe seizures. The longest duration of asystole previously reported is in a 17 year old man with temporal lobe epilepsy who sustained a 22 second pause in cardiac output. More typically the asystolic periods in documented cases are in the region of 5–10 seconds. Shorter duration asystole may not compromise cerebral function sufficiently to cause loss of consciousness. Implantation of a cardiac pacemaker is advocated but does not ensure that lapses of consciousness are eliminated if these are directly related to the seizure rather than to the secondary asystole. We report on a patient with epileptic cardiac asystole of 25 seconds duration demonstrated by prolonged simultaneous EEG/ECG monitoring which responded well to pacemaker insertion.

A previously well 34 year old right handed builder was referred with a 1 year history of fortnightly episodes of loss of consciousness. There was no associated warning, aura, chest pain, or palpitations and the patient was only aware of the episode once consciousness was lost. EEG/ECG monitoring performed at the time of a further episode showed asystole of 25 seconds duration. A pacemaker was implanted and no further episodes have been recorded in the 17 months since the implantation.

16 Channel ictal EEG (eight channels illustrated with ECG) showing electrographic seizure onset and subsequent bradycardia and asystole.

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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 unconscious, inaccessible, and motionless for 90 to 120 seconds. On two occasions he appeared confused and disoriented immediately before a collapse. During the period of unconsciousness he would demonstrate no involuntary movements, orofacial automatisms, or cyanosis but he would become pale and “ashen” while staring straight ahead with a glazed look. The duration of the episode his limb would return to normal and within 2 minutes he would have fully recovered. Unusually during one reported episode of unconsciousness he was seen to briefly extend the fingers of both hands.

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

The patient was then referred to the Emergency 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 temporoparietal area and the EEG amplitude generalised rhythmic <1Hz activity followed by marked attenuation of the EEG amplitude. The normal EEG activity consisted for 10 seconds (figure C). This was followed by tachycardia and more cause region stimulation to cause bradycardia. It was hypothesised that there is a loss of synchrony between the LSV and right atrium which delays atrial depolarisation so that the electrical wavefronts reach the ventricles at a slower rate, increasing the QT interval duration.

Interictally, patients with epilepsy seem no more likely than age and sex-matched healthy subjects to experience arrhythmias although in one study patients with epilepsy had a faster ventricular rate and a longer QT interval than controls by 4%. It is hypothesised that this is a result of lower vagal tone. 1. It has been hypothesised that there is a loss of synchrony between the LSV and right atrium which delays atrial depolarisation so that the electrical wavefronts reach the ventricles at a slower rate, increasing the QT interval duration.

Bradycardia was common to these episodes. Three episodes were captured on the ECG and each episode showed an ictal period of bradycardia. The ictal period on the ECG showed: a decrease in heart rate on right hemispheric inactivation. Experimental stimulation of the rostral posterior insular cortex in anaesthetised rats has been shown to induce tachycardia and more cause region stimulation to cause bradycardia. 

Recurrent absence epileptic seizures exist as a common clinical feature. 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 the study. Recording solely the ECG or the EEG may result in erroneous conclusions being drawn and insufficient or inappropriate therapy being instituted. Distinction between a primary cardiac arrhythmia and a secondary central arrhythmia is possible only with simultaneous EEG/ECG recordings.

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

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant disorder, the molecular basis of which is a 1.3 m 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 who developed respiratory failure and proximal muscle weakness who were prominent features.

The patient started to have dypsana on exertion at the age of 44. At the age of 47, he noted 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 Chiba Red Cross Hospital as an emergency patient with a coma due to CO2 narcosis (PCO2, 117.6, PO2, 64.0). Responding to mechanical ventilation support, he completely recovered consciousness within a day. His respiratory condition in the daytime improved to that previously. However, he needed mechanical ventilation during sleep because of nocturnal hypoventilation.

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

In a neurological examination, the patient’s mental state and cranial nerves were normal. Evidence of muscular atrophy and lumbar lordosis was found. The muscular atrophy was prominent in the shoulder girdle, intercostal muscles, paravertebral muscles, and pelvic girdle, and moderate atrophy was present in all four limbs (figure). There was moderate weakness of the shoulder and pelvic girdle and mild weakness of the distal limbs. The thorax showed poor respiratory movement, and the patient showed paradoxical movement of the abdomen in the supine position. Tendon reflexes were hyporeactive in all limbs. The patient’s sensations of touch and pain were mildly impaired in the four limbs. His position sense was normal. His vital capacity was 1.9 l (55% of the normal mean) in the sitting position, but 1.3 l (38%) in the supine position. The percentage of forced expiratory volume in 1 second was normal (99%) and was normal (99%) in the standing position. The lowest minute ventilation normal was 48 l. In the standing position, he had a respiratory function test and found a respiratory rate of 15 breaths per minute.

A 57-year-old man was admitted to the emergency department with 2 days of progressive weakness of the right lower extremity. The patient had a history of HNPP, which was diagnosed at the age of 13. He was admitted to the hospital with a diagnosis of myasthenia gravis, which was confirmed by electromyography and nerve conduction studies. Muscle biopsy showed a normal muscle biopsy. His respiratory condition in the daytime improved to that previously. However, he needed mechanical ventilation during sleep because of nocturnal hypoventilation.
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 femoritis, 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 tomacular 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 experienced generalised hyporeflexia or areflexia but no weakness or sensory loss, and nerve conduction studies showed moderate conduction slowing with accentuation at the common entrapment sites, suggesting demyelinating neuropathy.

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

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

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Spinal accessory neuropathy and internal jugular thrombosis after carotid endarterectomy

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

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

We report on a patient who developed right spinal accessory neuropathy and internal jugular venous thrombosis after right CEA. A 59 year old man underwent right CEA for possibly symptomatic stenosis. Angiography had shown 90% stenosis of the right internal carotid. The operation was done under general anaesthesia. The carotid bifurcation was unusually distal, necessitating a long dissection and high retraction. No immediate postoperative complications were evident. The next day, the patient complained of mild pain at the operative site, but he did not notice any weakness. The pain spread into his right shoulder within several days; at that time, he also noted difficulty raising his right arm. His symptoms worsened further a few weeks later. The symptoms persisted, and he presented for neurological evaluation 4 months after CEA. At that time, he had some induration along the incision site and a palpable cord within the right supraclavicular fossa. There was moderate atrophy of the right sternocleidomastoid and trapezius, with right shoulder drooping and minor right scapular winging. Right arm abduction produced more prominent scapular winging and was limited to 90 degrees due to pain and weakness. Electrodagnostic studies were consistent with partial right accessory neuropathy with minor denervation of the right trapezius. Cervical ultrasonography and MRI demonstrated right internal jugular venous thrombosis. The patient was treated with a shoulder support, analgesics, and low dose aspirin. There was no significant clinical change 1 year after CEA. Repeat electrodagnostic studies were consistent with chronic right spinal accessory neuropathy, and repeat ultrasonography showed persistent right internal jugular venous thrombosis.

Symptomatic spinal accessory neuropathy was first reported as a complication of CEA in 1982. Since then, there have been several case reports and small series.1 A 1996 review of reports of cranial neuropathy after CEA disclosed only one patient with spinal accessory neuropathy in over 3000 cases.1 Although the authors did not include several other reports2 3 which, taken together, may seem to suggest a somewhat higher incidence, the overall small number of reported cases in proportion to the hundreds of thousands of CEAs that have been done worldwide suggests that clinically significant spinal accessory neuropathy is a rare complication. Most spinal accessory neuropathy after CEA may be more frequent. The cause of spinal accessory neuropathy after CEA is usually not well established, but intraoperative nerve stretching or compression from retraction is most often invoked.4 Delayed onset (after 3 weeks) has been noted in some; for these patients, postoperative inflammation and scarring seem more likely causes. Spinal accessory nerve transection or ischemia/infarction (arterial or venous) are other possibilities. As in our patient, high carotid dissection and retraction have been reported to precede spinal accessory neuropathy.1 4

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

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

The presence of induration about the incision site and a palpable supraclavicular cord in our patient led us to suspect venous thrombosis. Internal jugular venous thrombosis may often be asymptomatic. Potential symptoms of internal jugular venous thrombosis include headache, dysphagia, and ante-rolateral neck pain, tenderness, and swelling. In addition to perivenous induration, fever and leukocytosis may occur.5

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

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

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

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

The patient had no vascular risk factors, in particular no tobacco use, and he was perfectly fit until his stroke. He was a sportsman with 2 hours daily intensive training for body building. He was working as a baggage handler in an international airline company. During a recent journey to Miami, Florida, he bought tablets of “energy pills” in a shopping store to enhance his athletic performances. The first drug contained MaHuang extract (corresponding to 20 mg ephedra alkaloids), 200 mg caffeine, 100 mg L-carnitine, and 200 µg chromium per two capsules. The second drug contained 6000 mg creatine monohydrate, 1000 mg taurine, 100 mg inosine, and 5 mg coenzyme Q10 per scoop. He consumed 40–60 mg ephedra alkaloids, 400–600 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 excluded as he recently returned from a transatlantic flight, there was no deep venous thrombosis and D-dimers were normal. However, ephedrine has an indirect sympathomimetic action mainly via 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.1 Ephedrine and its metabolites are natural products that are used in non-prescription medicines for multiple uses in the United States, intract, which contains ephedrine, is used among young sportsmen and sportswomen as an energy supplement in non-prescription tablets in some countries.

Although no cardiovascular 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.1

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

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

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Petroclival meningioma as a cause of ipsilateral cervicofacial dyskinesias

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

A 32 year old left handed woman complained about left sided facial dysaesthesia of the upper quadrant of her face for 1 year. In addition she had intermittent ipsilateral headache. A left sided facial palsy and hypogeusia developed. When progressive hearing loss and persistent ipsilateral tinnitus occurred she sought medical advice. She was referred to our department for further treatment after a large tumour in the left cerebellopontine angle had been demonstrated by MRI. On admission, the left corneal reflex was absent. There was marked hypoaesthesia of the first two divisions of the left trigeminal nerve and a mild left facial palsy. There was also hypogeusia of the left half of the tongue. Speech was slightly dysarthric. During examination dystonic and choreic movements of the left facial muscles were seen. The dystonic grimacing increased when the patient was being observed. There were also intermittent jerky dystonic head movements with turning of the head to the left, associated with slight elevation of the left shoulder. The facial movement disorder was clearly different from hemifacial spasm. There were no tonic or clonic synchronous contractions of facial muscles and no signs of involuntary coactivation. The patient barely noted the dyskinesias. Audiometry showed a hearing threshold at 30 Db on the left side and lack of stapedius reflex on the left side. Oculovesicular response to caloric stimulation was

(A) Axial T2 weighted SE MR images of a 32 year old woman with left sided cervicofacial dyskinesias show a large left petroclival meningioma compressing the brainstem. (B) Coronal inversion recovery MR scans demonstrate marked displacement and distortion of the brainstem due to the petroclival meningioma. (C) Gadolinium enhanced axial T1 weighted SE MR scans 3 months postoperatively show complete removal of the tumour and normalisation of the displacement of the brain stem.
decreased on the left side. Furthermore, there was mild left dyslochokinesia.

Neurography of the facial nerve was normal on both sides. Needle myography of the left frontalis and orbiculari oculi did not show signs of denervation.

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

The progressive improvement of the dystonic and choreic grimacing and the cervical dystonia indicates a causal association between the petroclinoidal meningioma and the segmental hyperkinetic movement disorders. Such a relation is strongly supported also by the absence of a family history of movement disorders and the absence of previous exposure to neuroleptic medication. Hyperkinetic movement disorders due to tumours of the brainstem or of the posterior fossa have been reported only rarely. Asymmetrical blepharospasm was recently found in a patient with an ipsilateral mesencephalic cyst. 7 Hemifacial spasm was seen in patients with paroxysmic neumonias, myositis. 1 , and epidermoid tumours of the cerebellopontine angle. 7 Acoustic neumonias and anaplastic pontocerebellar glioma can be associated with facial myokymia and spasatic parietic facial contracture. 1 Also, cervical dystonia due to tumours of the cerebellopontine angle have been reported recently. 7

The pathophysiological mechanisms responsible for dystonic movement disorders caused by structural or functional lesions of the brainstem are not fully understood. The possibility of denervation supersensitivity of cranial nerve nuclei has been proposed previously. Alternatively, enhanced excitability of brainstem interneurons has been suggested. 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. 7 Our case provides further evidence that functional impairment by compression and distortion of the brain stem may cause hyperkinetic cervicofacial movement disorders. It is not 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 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 leukocyte extract which is assumed to transfer cell mediated immunity in an antigen specific fashion. 3 The mechanisms of action of transfer factor are still far from clear; in vitro dialysable leukocyte extract increases macrophage activation and interleukin (IL) 1 production and enhances leukocyte chemotaxis and natural killer function. Transfer factor has been reported to stimulate the cell mediated antigen specific response in patients with various infections; 4 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. 5 Administration of dialysable leukocyte extract has seemed to be free of hypersensitivity, long lasting side effects, or complications, except for transitory hyperpyrexia. 3

We report on a patient in whom multiple cerebral white matter lesions developed after taking dialysable leukocyte extract orally for uveitis. A 28 year old man was admitted to hospital because of headache, mental confusion, and right hemiparesis. He had had recurrent bilateral uveitis from the age of 12 to 14 with relapse of right eye. In January 1995 retinal vasculitis was diagnosed at fundoscopy and in July 1995 he started oral transfer factor as dialysable leukocyte extract twice a week. He complained of generalised weakness after the second dose and the referring symptoms developed after the third dose.

Neurological examination on admission showed mental confusion and severe right spastic hemiparesis with 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 titer (355 UI/ml, normal <200 UI/ml), and anticyclic Ig G (30 UI/ml, normal 140 UI/ml). Negative results were obtained for toxoplasma and varicella zoster virus, toxoplasma gondii, toxoplasm gangliar, and hepatitis A and B 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, toxoplasma gondii, the Paul Bunnel reaction, anti-HIV, and the markers of hepatitis B and C infection were negative.

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

The patient had a progressive spontaneous remission of symptoms and signs. The neurological examination 20 days after onset showed slightly increased deep tendon reflexes on the right side and was normal 40 days later; all laboratory analyses were normal except for antistreptolysin titer (265 UI/ml). Two MR scans at 1 and 4 months after onset showed progressive reduction of the extension of cerebral white matter lesions, which did not show contrast enhancement. A final MR scan 20 months after onset showed further regression of lesions without contrast enhancement 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 leukocyte extract therapy and appearance of cerebral white matter lesions in our patient supports the possibility that the association of the two events might not be 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 anticytoplasm antibodies is found in 2% of healthy subjects.1 The occurrence at different time of focal cerebral white matter lesions highly supports the diagnosis of multiple sclerosis, but some clinical and laboratory findings in the patient are not typical for this condition. Mental confusion is not common at the onset of multiple sclerosis whereas it is often found in infections such as during vaccinations or viral infections. 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 imprecision of fine finger movements, dysgraphaesthesia on sensory testing, and a manneristic gripping handshake. There were no extrapyramidal symptoms. The patient was hyperactive and distractible. There were no extrapyramidal movements, dysgraphaesthesia on sensory testing, and a manneristic gripping handshake. There were no extrapyramidal symptoms.

Brain CT, axial section: dense calcific deposits in the basal ganglia, thalamus, and orbitofrontal cortex consistent with Fahr’s disease.
symptoms. His IQ score was in the low range (WISC-C=85 at the age of 13; Bar-Beau- Pinard =82 at the age of 17). He also presented an impairment on the Tower of London test, which measures executive function, and in a task assessing the understanding of other's intentions. These two findings are reliably present in pervasive developmental disorders, in this IQ range. In addition, his performance on the Tower of Toronto test disclosed impaired performance in procedural learning. 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 behaviour. Nevertheless, he did not present delay in language acquisition or morphological atypicalities in language development, which corresponds to DSM-IV criteria for Asperger’s syndrome.

Brain CT showed dense calcium deposits in the basal ganglia, thalamus, cerebellar dentate nucleus, and orbitofrontal cortex, consistent with Fahr’s disease (figure). Six weeks after CT, there was 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 0.70–1.30 mM), ionised calcium was 0.80 mM at pH 7.4 (normal 1.10–1.34 mM); urinary calcium was 0.8 mM (normal 2.5–6.3 mM). Serum parathyroid hormone was below 0.6 (normal 1.0–6.55 pM), 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 disorder are scarce and inconclusive.1 Although the tempo-occipital region is the most often involved in pervasive developmental disorders2 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.3 Abnormal cell counts and morphology in the cerebellar hemispheres have also been reported, but the relation of these findings to autism is controversial.4 Fahr’s disease consists of symmetric calcifications, located mainly in the basal forebrain and cerebellum, which are of various astrocytologies. Cognitive and behavioural abnormalities may be present when calcifications occur early in development. A fortuitous association between pervasive developmental disorder and hypocalcemia, given the paucity of published cases, is plausible in the presented patient. Nevertheless, our case suggests that abnormal phospho-calcium metabolism could produce an autistic syndrome when brain calcifications cause specific neuropsychological deficits, due to their localisation. For example, errors of social judgement may be related to calcifications of the orbitofrontal cortex, whereas dysfunction of frontal-basal ganglia circuits may contrib-
Selective hemihyposmia due to tentorial coup injury against dorsolateral midbrain: potential cause of sensory impairment after closed head injury

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

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 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.1,2 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.1,3 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.1,3,12 The clinical manifestation of our patient may represent one of the mildest forms of the midbrain contusion. Therefore, when we see a patient with post-traumatic sensory deficit, the possibility of this tentorial injury should be kept in mind even in minor head injury.


The MR images in our case showed a discrete lesion at the left dorsolateral midbrain. Topographical study at this lower midbrain level showed that the lateral and ventral spinothalamic and ventral trigeminothalamic tracts pass at the surface of this level by carrying a superficial somatosensory input.1 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 are 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.

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Toluene induced postural tremor

We read with interest the article by Miyagi et al1 and comment on the medical treatment of toluene induced tremor. Microdialysis experiments in rats have shown that inhalation of toluene increases extracellular γ-aminobutyric acid (GABA) concentrations within the cerebellar cortex1 which probably explains why GABA agonists including benzodiazepines (for example, clonazepam) are not very effective in toluene induced tremor and ataxia. Rat experiments also showed a 50% reduction in brain catecholaminergic neurons.2 Degeneration of certain cerebellar pathways is probably responsible for the loss of this dopaminergic innervation.3 Dopamine agonists could therefore be of potential interest in the treatment of toluene induced tremor. This hypothesis was explored in a recently described case, which showed remarkable clinical and iconographic similarities with that described by Miyagi et al.: (a) long history of chronic toluene inhalation, (b) marked postural tremor, (c) progressive worsening of the symptoms despite 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 in patients of heredodegenerative disorders in which the dentatorubro-olivary system is affected. In addition, there is evidence that catecholaminergic pathways are also involved in this type of ataxias, supported by loss of function of these neurotransmitters in the CSF of patients with heredodegenerative ataxias.4 In our patient, amantadine hydrochloride (100 mg twice daily) abolished postural tremor and ataxia completely over a 3 month period. Subsequently, the treatment was discontinued, which resulted in relapse of tremor and ataxia. He was rechallenged to amantadine, which progressively offered him the same clinical improvement as in the first 3 months. After 3 years the treatment was discontinued without any sign of relapse.

Although this finding needs confirmation, amantadine treatment could form a new approach in the medical treatment for toluene induced tremor and ataxia. Intractable cases would then justify a more aggressive approach such as ventrointermedius thalamotomy.

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3 Bjorvogt S, Naalsund L. Biochemical changes in different brain areas after toluene inhalation. Toxicology 1989;49:36.

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

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

Identifying the risk factors that can tell us 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 suggests some new hypotheses but does not eliminate 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.


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 and upper limbs and little or no effect of either a bulbar nature or in the lower limbs. Thus Hu et al3 coined the term fetal 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 ALS who had a typical bulbar or upper motor neuron syndrome, with severe proximal and varying degrees of distal involvement, calling it amyotrophic brachial diplegia syndrome. Other terms used in the past to refer to this form of ALS have been dangling arm syndrome, suspended form, or orangutan sign, dead arm sign, bifacial palsy, rizomelic amyotrophy, and the idea of naming it a distinctive phenotype of a neurogenic amyotrophy with a characteristic clinical picture.

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Sasaki replies: We thank Gamez et al for their interest in our article concerning the atypical form of amyotrophic lateral sclerosis (ALS).

Over many years, several researchers have recognised this peculiar distribution of muscle atrophy in clinical practice. The clinical manifestations consist of the muscular atrophy confined to the chest girdle and the arms (proximally dominant), absence of deep tendon reflexes in the arms, normal reflexes in the legs, and subluxation of the shoulder joints. Some patients progress to bulbar involvement. As Gamez et al cite, many terms have been coined to describe this peculiar pattern of the muscular atrophy such as flail arm syndrome, or isolated dysarthria because of no muscle atrophy on the diaphragm and the respiratory muscle failure occurs much later than in the typical form of ALS. This can be seen in the follow up of the results obtained in the respiratory function tests (FVC, FImax, and PEmax).

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

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

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

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Isolated dysarthria

We read with interest the article by Urban et al. Using transcranial magnetic stimulation, the authors demonstrated electrophysiological evidence for a central monoparesis of the tongue in patients with isolated dysarthria from stroke.1 As in their patients transcranial magnetic stimulation induced absent or delayed corticobulbar responses at the tongue, the authors ascribed isolated dysarthria to interruption of the corticobulbar pathways. On the whole it is not plausible, but we would like to comment on the underlying mechanism of isolated dysarthria.

As in the case of isolated dysarthria reported by Urban et al, all of our patients with isolated dysarthria had lacunar infarctions involving the internal capsule and corona radiata.2 Measurement of cerebral blood flow with IMP-SPECT in these patients disclosed frontal cortical hypoperfusion, particularly in the anterior opercular and medial frontal regions. Anterior opercular lesions produce facio-pharyngeal-glossomandibular paresis (anterior opercular syndrome), and damage to the medial frontal regions, including the supplementary motor area, causes speech expression disorders. White matter lesions can disrupt afferent and efferent fibre connections in subcortical language areas, resulting in dysfunction of these cortices.3 Therefore, we postulated that isolated dysarthria results from interruption of corticobulbar networks indispensable for speech output, involving the thalamocortical and corticospinal fibres as well as the corticobulbar fibres. In fact, lacunar infarctions around the internal capsule-corona radiata are likely to undercut these ascending and descending pathways.

To assess corticopontocerebellar tract function, Urban et al investigated cerebellar blood flow in patients with isolated dysarthria using HMPAO-SPECT. They concluded that the corticopontocerebellar tract is preserved 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 supported frontal cortical dysfunction as an underlying mechanism of isolated dysarthria. Lingual hypoperfusion was evident in three of seven patients reported by Urban et al and in two of 12 by us. This indicates that isolated dysarthria originates in incoordination of multiple organs necessary for speech articulation as well as cerebral diaschisis. Although interruption of the corticobulbar pathways is a likely cause of isolated dysarthria, it should be borne in mind that damage to other descending and ascending projections may contribute to isolated dysarthria.
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 their results, we previously found a reduced intracortical inhibition in a group of patients with genetically confirmed Huntington's disease. Hanajima et al. suggest that the discrepancies between the two studies were due to methodological 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 correlation with a dyskinetic rating scale, had a more advanced stage of the disease possibly with coexisting dystonia or rigidity. These assertions deserve some comments.

The mean disease duration of our nine patients with Huntington's disease was 6.2 (4.1) years which is actually shorter than the duration of the six patients reported by Hanajima et al. (8.3 (5.9) years). Most of our patients could be considered in an early stage of the disease, the Unified Huntington's disease rating scale, and none presented dystonia, rigidity, or any other additional movement disorder. In this regard, however, it should be pointed out that bradykinesia is often associated with chorea in patients with Huntington's disease and may even precede the appearance of choreic dyskinesia. Chorea itself is often reduced in the more advanced Huntington's disease stages. It is unlikely, therefore, that any neurophysiological 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 patient. We were not really surprised at the results of Hanajima et al., but 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 progression as we did not find any change in four patients, two of them already reported, with positive DNA testing but completely asymptomatic.

The discrepancies between the two studies are more likely to be explained, at least in part, by some methodological differences. For instance, the amplitude of the control response was larger in our set (approximately 1.0 mV compared with 0.3 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) than in the study of Hanajima et al.

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

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intracortical inhibition is often decreased even in normal subjects. The 50% of the threshold for relaxed muscles must correspond to different values relative to the threshold for active muscles in patients from that in normal subjects. (2) The intracortical inhibition is delay in Doppler spectra of arteries with a high vascular resistance (peripheral arteries, middle cerebral artery during strong hypocapnia). In the case of ABP<CCP and a small vessel collapse according to the model of the authors, CVR should increase towards 1 and FV towards zero (equation 1). Negative flow values could, consequently, not occur.

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

\[ FV = (ABP - ICP)/CVR \]

and equation 5 to

\[ \text{CPP}_2 = \frac{0.5 \text{ABP} + 0.5 \text{ICP}}{0.5 \text{CVR}_1 /0.5 \text{CVR}_0} \]

The final issue concerning negative flow velocities is a trap Diehl has raised. It is a well-known fact that the vascular impedance (or ICP was not always constant, CCP should decrease. A point worth mentioning is that critical closing pressure. From the definition, the formula proposed by Michel et al. is very similar. The only difference is that instead of the original waveforms of FV and ABP, first (fundamental) harmonic components were taken for the same graphical construction—that is

\[ \text{CPP}_2 = \frac{\text{ABP} - \text{ICP}}{0.5 \text{CVR}_1 /0.5 \text{CVR}_0} \]

In our paper we confirmed empirically that both CCP1 and CCP2 produced the same values in a group of patients after head injury, therefore the mathematical consideration of Diehl (equations 1–5) must contain an error!

First of all we cannot see how equation (1) from Diehl’s letter can be derived from any of our formulae. Everyone who has tried to plot momentary values from ABP pulse waveform against momentary values of FV waveform knows that it never plots a straight line (equation (1) implies). I suggest that the relation between pulsatile pressure and flow should be better described using the concept of static and dynamic resistances (CVR0 and CVR1). The driving pressure of the mean flow is more accurately given by cerebral perfusion pressure (CPP) than by ABP-CCP. Therefore, equation 2 changes to

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The final issue concerning negative flow velocities is a trap Diehl has raised. It is a well-known fact that the vascular impedance (or ICP was not always constant, CCP should decrease. A point worth mentioning is that critical closing pressure. From the definition, the formula proposed by Michel et al. is very similar. The only difference is that instead of the original waveforms of FV and ABP, first (fundamental) harmonic components were taken for the same graphical construction—that is

\[ \text{CPP}_2 = \frac{\text{ABP} - \text{ICP}}{0.5 \text{CVR}_1 /0.5 \text{CVR}_0} \]

In our paper we confirmed empirically that both CCP1 and CCP2 produced the same values in a group of patients after head injury, therefore the mathematical consideration of Diehl (equations 1–5) must contain an error!

First of all we cannot see how equation (1) from Diehl’s letter can be derived from any of our formulae. Everyone who has tried to plot momentary values from ABP pulse waveform against momentary values of FV waveform knows that it never plots a straight line (equation (1) implies). I suggest that the relation between pulsatile pressure and flow should be better described using the concept of static and dynamic resistances (CVR0 and CVR1). The driving pressure of the mean flow is more accurately given by cerebral perfusion pressure (CPP) than by ABP-CCP. Therefore, equation 2 changes to

\[ FV = (ABP - ICP)/CVR \]

and equation 5 to

\[ \text{CPP}_2 = \frac{0.5 \text{ABP} + 0.5 \text{ICP}}{0.5 \text{CVR}_1 /0.5 \text{CVR}_0} \]

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risks. How risky—we can see from Diethl's letter. Cerebrovascular resistance certainly never increases to infinity, only after death.

We fully agree with the considerations regarding equations (6) and (7). CCP can be understood as a combination of ABP and ICP with conflicting properties in the cerebrovascular bed. Whether it simplifies our knowledge—we personally find it doubtful.

Finally, we are truly obliged to Diethl 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 sub-
thalamic nucleus leading to diminished exci-
tation of the globus pallidum internum is associated with chorea-ballism in animals.1 Levodopa induced dyskinesias are currently thought to share a similar pathophysiology2 but recent findings also suggest that abnor-
mal patterns of neuronal firing in the globus pallidum internum may be of relevance.3,4

Data from both parkinsonian monkeys and patients with Parkinson’s disease submitted to lesion5 or functional blockade of the sub-
thalamic 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.6 The case recently described by Figueras-Mendez et al 7 is extremely interesting as it suggests that func-
tional inhibition of the subthalamic nucleus by high frequency stimulation blocks levodopa induced dyskinesias. This is clearly at odds with the current pathophysiological model of the basal ganglia.8,9 Thus, the finding of Figueras-Mendez et al 7 rises the intriguing possibility that dyskinesias depend or are mediated by neuronal firing in a given region of the subthalamic nucleus, which was blocked by high frequency stimulation.

Measurement of afferent synaptic activity by the technique of 2-deoxyglucose (2-DG) uptake showed an increment in the subthalamic nucleus compatible with increased inhibition from the globus pallidum externum, particularly in the ventromedial tip of the nucleus.6 This contrasts with the findings in monkeys with chorea induced by pharmacological blockade of the globus pallidum externum, in which 2-DG uptake was maxi-
mal in the dorsolateral portion of the subtha-
lamic nucleus, where the sensorimotor region lies. A recent anatomical study8 also showed that the cortical-subthalamic pathways 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.8 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 used to sustain the idea that the high frequency stimulation of the subthalamic nucleus in the region of levodopa induced dyskinesias, there is a cru-
tial 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 electro-
trode: (1) Stimulation of the subthalamic nucleus in Parkinson’s disease has been asso-
ci ated with the production of dyskinesias only with relief reduced in levodopa intake.10 Moreover, Benabid et al who pioneered this technique, consider the induction of dyskine-
sias by high frequency stimulation of the sub-
thalamic nucleus as a good indicator of a very positive response.7 Further, the effect on the subthalamic nucleus from the globus pallidum internum is placed dorsocaudally to the subthalamic nucleus and could be blocked by high frequency stimulation. (2) When the record-
ing electrode is positioned laterally postsynaptic to the subthalamic nucleus, neuronal activity is characterised by action potentials of large amplitudes (0.5–1 mV) with low background activity, tonically firing neurons, and absent sensori-

motor responses (“driving”). All these char-
acteristics were seen 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 docu-
ment 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 differ-
ent recording tracks, the effects of micros-
timulation, and the post surgery MRI with measurement of the tip of the electrodes. If, as assumed, the subthalamic nucleus was indeed correctly targeted in this patient, the pathophysiology of the basal gan-
glia will need to be revisited.

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low background activity found in our recordings is only due to the better signal-to-noise ratio of the electrodes used. “Good recording electrodes” depend on many variables such as tip size, tip profile, insulation material, impedance, manufacture, etc. The signal-to-noise ratio of the cells in question has the same ratio as the subthalamic nucleus cell shown by Hutchinson et al. In our report, cells discharged tonically, burst discharges of tremor. The stimulator resulted in a tremor-like movement. These and other vascular effects of statins in cerebral ischaemia are potentially of great importance in human neuroprotection and ought to be the subject 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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NITRIC 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. 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 above-mentioned neuroprotective effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or “statins” in cerebral ischaemia. Preliminary studies have shown that statins modulate brain nitric oxide synthase (NOS) activity in a neuroprotective manner. Data from a murine model of ischaemic stroke demonstrate that prophylactic statin therapy reduces infarct size by about 30%, and improves neurological outcome in normocholesterolaemic animals. In this investigation, statin therapy directly upregulated endothelial NOS in the brain without altering expression of neuronal NOS. Recent findings also suggest that statin therapy influences the activity of inducible NOS. Lovastatin has been shown to inhibit cytokine-mediated upregulation of inducible NOS and production of NO in rat astrocytes and macrophages, and this inhibition may represent a novel 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 ought to be the subject 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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BOOK REVIEWS


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

The intrusive authorial voice fell into disfavour in literary circles around the turn of the century because it was thought that alluding attention to the act of narrating might detract from realistic illusion, so reducing the emotional intensity of what was being represented. It is a device much favoured by postmodern writers, who expose the nature of fictional constructs. The intrusive medical author never dropped out of fashion, although in these days of evidence based prejudice, authorial omniscience might be considered suspect. The authors of this volume are intrusive in a guiding conversational manner that makes this book by far the most readable of the neuroimmunological texts.

The book opens with a highly accessible chapter on immunological requirements of the CNS. There follows a chapter that integrates the neurobiology of multiple sclerosis with contemporary issues of aetiology, cell injury, and repair. Next, a chapter on inflammatory demyelinating diseases examines syndromes of isolated demyelination, acute disseminated encephalomyelitis and allied conditions, and some of the syndromes of demyelination that are now accepted as part of the range of multiple sclerosis. The chapters on demyelinating disease are drawn to a close by a discussion of existing and experimental therapies for multiple sclerosis.

The book continues with chapters on para-neoplastic disorders of the CNS, stiff man syndrome, neurologically complications of
connective tissue disorders, organ specific autoimmune, sarcoidosis, and cerebral vasculitis. Each chapter is an appropriate length and well referenced; the wood is always clearly visible between the trees. The book is sufficiently readable and small to be recommended as a holiday reading. Its only drawback is that in making erudition so readily available, one risks being outshined yet again by one's registrar.

JON SUSSMAN


As Alzheimer’s disease becomes of increasing importance to society, basic science research in this field needs to provide the building blocks for both therapeutic interventions and accurate diagnosis. This publication is a collection of papers presented at an international Alzheimer’s disease research meeting in Leipzig in 1997. This conference aimed to bring together both clinical and basic science disciplines and this is reflected in the papers selected for this book. There are 31 papers included, covering topics from early symptomatology and cognitive features to immunobiology and theoretical neuronal treatment strategies. The contributors to this book are some of the most authoritative in their field, predominantly based in Europe. Covering all aspects of Alzheimer’s disease research from the correct diagnosis to basic science approaches of treatment is ambitious for such a compact book (315 pages), and although the editors succeed in collecting an interesting series of papers around these themes, they make no claims to be comprehensive in their scope. The papers included range from individual research reports to reviews of the current literature. The review papers are generally excellent, concise, clear, well referenced, and illustrated—for example, there are excellent reviews of Alzheimer’s disease with vascular pathology (Pasquier et al.), and Lewy body disease (McKeith et al.), great updates on neuropathology (Jellinger and Bancher, Braak et al.), and several worthy reviews of treatment strategies for Alzheimer’s disease including NSAIDs (Möller), antioxidants, and radical scavengers (Rösler et al.). I found the review by Reisberg et al on ontogenic models in the understanding of the management of Alzheimer’s disease particularly interesting. However, the papers of original research are of more limited interest to the general reader. Although, as mentioned, the quality of illustrations is good, there is some variability in the definition of abbreviations and occasional lapses into other European languages. Certainly, I think this book would be of value for investigators interested in the neuropathology, immunopathology, and molecular biology of Alzheimer’s disease. It would make an excellent addition to libraries as a reference text for many researchers of varied interests.

CLARE GALTON


Organ transplantation, once medical exotica, is now almost routine. In the United Kingdom each year are performed cadaveric organ transplants of about 1800 kidneys (in addition to 160 live kidney donors), 700 livers, and 450 heart/lung (UK Transplant Support Service). Several techniques for both immunosuppressive and surgical techniques were established at the beginning of the century in canine models. Translation of these experiments to humans awaited safe and effective immunosuppression. Until recently, forms of immunosuppression were radiation (total body or total lymphoid) and non-selective chemical reagents (benzene and tolenuene). Then the antiproliferative drug 6-mercaptopurine (6-mercaptopurine) was introduced, shortly followed by a derivative, azathioprine, with improved oral bioavailability. Combined with corticosteroids, these allowed the first human solid organ transplants to be performed: in 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 the increasing success of organ transplantation rests mainly on improved immunosuppression with drugs that selectively suppress lymphocytes by inhibiting lymphokine generation (cyclosporin A, tacrolimus), signal transduction (sirolimus, deoxyspergualin), or differentiation (15-deoxyspergualin) pathways. As a result, over the last 10 years in the United Kingdom, the 1 year survival of grafts has improved from 80% to 90% (kidney), 55% to 75% (liver), and 70% to 90% (heart/lung). Wijdicks estimates that 10% of transplant patients have a significant neurological complication with no common 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 series on Practical Neurology. The 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. Since typographical errors and mistranslations detract a little further from a book which seems unlikely to appeal to most neurologists, although it will no doubt be a source of reference to those working in the field of cognitive disorders, particularly vascular dementias.

PETER MARTIN


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

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

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

The book is essentially a collection of monographs of heterogeneous content and style and the result, perhaps not surprisingly, is that some of the component parts are better than the sum. The clinically oriented section 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 infancy 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 relation remains to be established. The chapters covering basic neurophysiology, neurochemistry, and neuropathology, are erudite and fascinating but at times are barely comprehensible. Further work is needed, including answering the fundamental question—why does the first seizure occur—before the clinician and basic scientist are able to talk the same language— for the benefit of the patient with epilepsy.

The concept of Childhood Epilepsies and Brain Development is innovative and commendable and overall the majority of the monographs are interesting and informative, the overall impression is that the individual parts (the chapters) are better than the whole (the book). The lack of an index is a strange omission, perhaps reflecting a prolonged editorial atypical absence, and although this militates against it becoming a well thumbed reference text, the book is an erudite addition to the mosby fibre-like sprouting of the epileptological literature.

RICHARD E APPLETON


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

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

The second half of the book is more of a mixed bag, both in terms of the areas covered and the quality of the chapters. Each chapter 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 say the treatment of affective illness (22 pages) or obsessive-compulsive disorder (15 pages). The brevity is only partly explained by the undeveloped state of that particular area of psychopharmacology. Sections on new or controversial antipsychotic agents and their impact on conventional antipsychotics, labelled electroconvulsive therapy, or new developments in brain imaging are e.g. no longer available for a busy junior doctor. There is no index.

These quibbles apart, prescribing guidelines can be wholeheartedly recommended.
Hypertrophic atlantoaxial ligaments: an unusual cause of compression of the upper spinal cord

ALEJANDRA TERESA RABADAN and GUSTAVO SEVLEVER

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