LETTERS TO THE EDITOR

Postictal psychosis related regional cerebral hyperperfusion

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

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 Antiepileptic drugs were withdrawn to facilitate seizure recording.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

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

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

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

Both patients showed postictal psychosis and had a regional increase in rCBF over the right temporal neocortex and the left basal ganglia compared with their interictal study (figure). Quantitative analysis for patient 1 showed changes of ASI during IP, PP, and over right MT was +75% (+6.64476 to -1.65289); over the right LT was +116.7% (1.07927 to 12.55764); and over the left BG was +206.8% (+2.07373 to 2.21574). Quantitative analysis for patient 2 showed changes of ASI during IP and PP over right MT was +3.8% (13.14217 to 12.64158); over right LT was +178.6% (10.4696 to 18.7057); and over left BG was +159.5% (-5.85556 to 3.27522).

Postictal psychosis is a distinct clinical event associated with temporal lobe epilepsy. The diagnosis of postictal psychosis requires a close temporal relation between bouts of complex partial seizures and the onset of psychosis. The psychosis usually develops after a cluster of complex partial seizures precipitating the onset of psychosis (PP) were analysed visually and in our laboratory, we found to work on fresh frozen material. According to the previous characterisation, the BC-1 isoform was present in the extracellular matrix. Their expression is dependent on enlargement of the venous compartment, organisation in the setting of angiogenesis. The staining was localised either in the endothelium or the subendothelial layer. A positive response was found in several arteries like vessels and in a few vessels with thinner walls. The BC-1 isoform was absent in the TN-11 Ab fragment showed occurrence of type III repeat C TN isoform in the inner layers of the vascular components of the nidus, irrespective of their morphology.

Six out of the 10 examined specimens were found to contain portions of cerebral tissue surrounding the angiomatic nucleus. In all these cases the wall of several vessels exhibited intense staining with the use of the TN-11 Ab fragment. Using the BC-1 Ab some of these vessels exhibited some staining (figure). In the control specimens (brain and cerebellum) both the FN isoform containing the ED-B sequence (ED-B-FN), and the type III repeat C TN isoform were absent, despite the widespread distribution of total FN and TN in the vascular walls.

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

<table>
<thead>
<tr>
<th>Anti-FN mAbs</th>
<th>Anti-TN Ab fragments</th>
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<tr>
<td>IST-4</td>
<td>Total TN</td>
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<tr>
<td>IST-9</td>
<td>BC-1</td>
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<tr>
<td>Widespread</td>
<td>Isoforms containing the ED-A sequence</td>
</tr>
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<td>Distribution of the isoform (s)</td>
<td>Widespread</td>
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| Tissue samples were obtained after neurological excisions of ruptured AVMs. All 10 patients had experienced an intracerebral haemorrhage as the first clinical manifestation of their disease. There was no drug history before bleeding. Control specimens from two right gyri recti and one cerebellar tonsil were obtained, respectively, from operations for ruptured aneurysms of the anterior communicating artery or for Arnold Chiari disease.

Immunohistochemical evaluations were performed on 5 µm thick cryostat sections using a protocol reported previously. Owing to the limited amount of available material, only in a few cases was some fresh tissue retained to allow western blots. Distribution of FN and TN isoforms was investigated using three monoclonal antibodies (mAbs) or two Ab fragments, obtained by phage display technology, respectively. These Abs, prepared in our laboratory, were found to work on fresh frozen material. According to the previous characterisation, the BC-1 mAb and the TN-11 Ab fragments are specific for isoforms occurring almost exclusively in fetal tissues and in tumours, with the recognised TN isoform being typically associated with anaplastic gliomas (table). Control sections were processed identically to the other specimens, but the primary antibody was substituted with a specific immunoglobulin of recombinant antibodies. The antibodies were blocked using the specific antigens. The antigens were recombinant protein containing the epitope produced in E Coli. For the mAb BC-1 we used the recombinant protein containing the type-III repeats 7B–8. For the mAb IST-4 we used the recombinant protein containing the type-III repeats 2–8. For the recombinant antibodies TN-11 and TN-12 the recombinant type-III repeat C and the recombinant fragment containing the BC-1 isoform were used.

All 10 AVMs were found to contain large amounts of FN and TN, as shown by intense immunostaining with the use of the IST-9 / IST-4 mAbs and the TN-12 Ab fragment. The staining was localised either in the endothelium or the subendothelial layer. A positive response was found in several arteries like vessels and in a few vessels with thinner walls. The BC-1 isoform was absent, despite the widespread distribution of total FN and TN in the vascular walls.
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 specific receptor tyrosine kinase is upregulated in the vasculature of arteriovenous malformations.

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 present findings indicate that a specific receptor tyrosine kinase is upregulated in the vasculature of arteriovenous malformations. 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.

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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 characterized 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 neuro-imaging. In most cases, the encephalopathy occurs without any gross change in circulating concentrations of thyroid hormones, suggesting that an inflammatory process is responsible for the cerebral dysfunction. In the absence of pathological data, the evidence for a specific pathogenetic mechanism is largely circumstantial: a small vessel vasculitis and immune complex deposition have both been suggested. Although none of the published cases of Hashimoto’s encephalopathy has described psychosis as a primary feature, it is possible that “myxoedematous madness”, a condition first described in detail by Asher in 1949 lies in a range of encephalopathic phenomena mediated by autoimmune mechanisms. This suggestion would certainly be consistent with the range of clinical presentations of other autoimmune cerebral vasculitides. As autoimmune thyroiditis is the commonest cause of thyroid failure in this country, it is likely that theseHaveva et al. have been present in at least some of Asher’s original 14 cases. Although most had florid myxoedematous features at psychiatric presentation, this may simply reflect the difficulty 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 police. His business had been in decline for several months, and his family had noticed uncharacteristic emotional lability. In the weeks preceding admission he had experienced delusions and hallucinations, and exhibited uncharacteristic behaviour. He had reported a vision of the crucifixion, and hearing the voice of his dead mother. He claimed that his house was occupied by the devil, drove around aimlessly in his car, and appeared constantly fearful and withdrawn. On the day of admission he had made a bonfire in the garden and burned his wife’s clothes, family photographs, furniture, and business papers. When his wife and son tried to intervene he
became aggressive and threatened them with a saw. The general practitioner was called and suspected although bought a new psychometric and was a severe depressive illness. Police assistance was requested because of the patient's continuing violent behaviour.

On admission he was unimpaired but cooperative and had bought a new psychometric and was a severe depressive illness. Police assistance was requested because of the patient's continuing violent behaviour.

In summary, therefore, this patient presented in clear consciousness with a first episode of acute psychosis, and evidence of subtle executive and linguistic neuropsychological disturbance, on the background of gradual behavioural and affective change. He was profoundly hypothyroid due to an autoimmune thyroiditis, and there was no clinical evidence of thyroid failure other than the normal mental state. 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 thyroidoencephalopathy. 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 rapid progressive mental and motor deterioration. Involuntary movements occur in above 90% of the patients in the course of the disease, the most common being myoclonus. Other movement disorders range from tremor to chorea, dystonia and hemiballism. We report on 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.

Alien hand sign in Creutzfeldt-Jakob disease

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

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

A 70 year old, right handed Jewish man born in Argentina, living in Israel for the past 20 years, was admitted to the Neurology Department. Until a month before his admission, he was apparently healthy and helped in the accounting office of the village where he lived. His neurological illness had presented insidiously during the past month with unsteadiness of gait and frequent falls. He also manifested behavioural changes, became aggressive, and had visual hallucinations, perceiving insects and mice moving through his visual field. Often, he expressed his fear from seeing that the “ceiling was...
falling over him”. His wife mentioned bizarre, useless movements of his left hand which were present from the beginning of the disease.

On admission, he was awake, bradyphrenic, and partially collaborative. His conversation, haemodynamic parameters and mental status were normal, as were folic acid, vitamin B12 levels, and the laboratory data including blood chemistry, electrolytes, creatinine, glucose, transaminase, bilirubin, serum albumin, copper, urinalysis, urinary porphyrin, folic acid, and vitamins A, B1, B6, B12, and E. Antibodies to gliadin, antiendomysium (AGAs), IgA antiendomysium, IgA antigliadin (AGAs), IgA antireticulum antibodies (EMAs), and IgA antigastric inclusion antibody (MGA) were negative. The cerebrospinal fluid had normal pressure. The cranial nerves were normal as were the facial and plantar responses. The right arm had a dystonic posture. His gait was ataxic on a wide base.

At times, the left arm would spontaneously rise in front of the patient during speaking or while using his right hand. He was unaware of these movements until they were brought to his attention. When questioned about their purpose, the patient denied that they were voluntary. No grasping of either hand or foot was found. The patient had no cortical sensory loss. The laboratory data including blood chemistry, electrolytes, creatinine, glucose, transaminase, bilirubin, serum albumin, copper, urinalysis, urinary porphyrin, folic acid, and vitamins A, B1, B6, B12, and E. Antibodies to gliadin, antiendomysium (AGAs), IgA antiendomysium, IgA antigliadin (AGAs), IgA antireticulum antibodies (EMAs), and IgA antigastric inclusion antibody (MGA) were negative. The cerebrospinal fluid had normal pressure. The cranial nerves were normal as were the facial and plantar responses. The right arm had a dystonic posture. His gait was ataxic on a wide base.

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

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

In CJD, bilateral cortical damage to motor areas might be the origin of their subsequent isolation and disconnection. We suggest that CJD should be added to the differential diagnosis of diseases presenting with an alien hand with or without myoclonus.

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

Correspondence to: Dr Dr R Inzelberg, Department of Neurology, Hillel Yaffe Medical Center, Hadera, Israel


Recent 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 in accordance with the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) 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, food she 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 few 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, creatinine, electrolytes, creatinine, glucose, transaminase, bilirubin, immunoglobulins (Igs), lead, iron, copper, urinalysis, urinary porphyrin, folic acid, and vitamins A, B1, B6, B12, and E. Antibodies to Cryptococcus neoformans, Toxoplasma gondii, herpes simplex, HIV, hepatitis A, B, C, and D, CMV, Mycoplasma pneumoniae, adenovirus antibodies, specific and non-specific organ autoantibodies, IgA and IgG antigliadin antibodies (AGAs), IgA antitissue transglutaminase antibodies (tTG-AMA), and IgA antireticulin antibodies (ARRA), 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
from those with neurological involvement pre-
occurring within weeks.

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
immuned mediated attack to the myelin.
By contrast, wallerian and axonal degenera-
tion may be caused by vasculitis, and
nutritional, metabolic, and toxic factors.

An autoimmune pathogenesis in associ-
ation with strong evidence of a genetic
susceptibility has been proposed for celiac
disease. Although it is well established that
AGA, EMA, and ARA are reliable indicators
of sensitisation to gluten at least at the
time of diagnosis, in the clinical practice at
follow up, 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 conclusion, our case shows two major
issues: an acute polynueropathy can be
a complication of celiac disease in childhood
and its benign course could help in the
understanding of the underlying pathogenic
mechanisms.

Frontal release signs in older people
with peripheral vascular disease

A growing body of research examining
neurological aspects of clinically “silent”
 cerebrovascular disease suggests that
neurological signs indicative of generalised organic
brain damage may occur in the absence of
completed stroke.1 These soft signs include primitive reflexes (frontal release
signs), representing an anatomical and functional
deferreration of cortical from subcortical struc-
tures. Primitive reflexes are known to occur in
a wide variety of neurological conditions, including
Alzheimer’s disease3 and vascular dementia.4

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 peripheral disease found that 72 of
the 144 patients who had not experienced a
transient 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 popula-
tion of patients under investigation for
peripheral vascular disease.
examined using a rating scale for the examination of frontal release signs (FRRS), with nine operationally defined items, each on a seven point semi-quantitative scale. The nine reflexes were paratonia and palomental, hand grasp, foot grasp, glabellar, rooting, snout, and visual/tactile sucking reflexes. Neuropsychological measures included the assessment of frontal lobe function (trailmaking tests A and B, behavioural dyscontrol and central vascular pathology.

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

<table>
<thead>
<tr>
<th>Reflex</th>
<th>Hand grasp</th>
<th>Foot grasp</th>
<th>Glabellar</th>
<th>Palomental</th>
<th>Parotonia</th>
<th>Rooting</th>
<th>Snout</th>
<th>Sucking (tactile)</th>
<th>Sucking (visual)</th>
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<tr>
<td>U</td>
<td>274.0</td>
<td>312.5</td>
<td>199.5</td>
<td>287.5</td>
<td>287.0</td>
<td>235.5</td>
<td>287.5</td>
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<td>pValue</td>
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<td>1.0</td>
<td>0.001*</td>
<td>0.15</td>
<td>0.29</td>
<td>0.01*</td>
<td>0.44</td>
<td>0.08</td>
<td>0.30</td>
</tr>
</tbody>
</table>

*Higher mean score in people with peripheral vascular disease.

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

I thank Dr Robert Howard for supervision of this study and Professor Doreen Abas 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 M.D. thesis.

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Factitious clock drawing and constructional apraxia

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

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

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

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

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

Brain CT and MRI, CSF examination, and routine EEG were normal. Routine haemato-
logical and metabolic analyses plus erythrocyte sedimentation rate, serum lactate, pro-
thrombin time/paratime, and fasting serum glucose, HBa1c, serum Ig s,

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density low-density lipoprotein (3.92 mmol/l) and triglycerides (4.30 mmol/l) and high density lipoprotein (0.73 mmol/l). Serum phenytoin concentration was therapeutic at 74 µmol/l. An ECG was normal.

Ophthalmological consultation and formal visual field testing demonstrated a concentric constricted field of mild degree in the right eye and tunnel vision in the left eye. The patient consented to overnight video-EEG monitoring and was seen on multiple occasions to move his left arm and/or leg in a normal fashion, at one point using the left arm to readjust his bed covers shortly after arousal from sleep, before glancing briefly at the video camera and completing the task with his right arm. The prolonged EEG was normal.

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

Anosognosia and mania associated with right thalamic haemorrhage

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

A 53 year old, right handed, black man, with a history of alcohol misuse and dependence and untreated hypertension, was brought to the emergency room a few hours after developing an intense headache and left sided numbness and weakness. On admission he was described as "belligerent," "agitated," and "confused." Blood pressure was 240/160. Neurological examination disclosed left lower facial droop, decreased left corneal and gag reflexes, and left hemiparesis with dense sensory deficits. With increasing obtundation, the patient was transferred to the intensive care unit and intubated. Brain MRI showed a large, left sided, hyperacute thalamic bleed with mass effect and oedema. The patient was extubated 2 days later and 4 days after the stroke he was described as being drowsy and inattentive, but was able to answer questions.
appropriately. Neurological examination showed contralateral gaze preference, supranuclear vertical gaze palsy, difficulty converging, left sided faccial 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 extubated, the patient acknowl-
edged that he had had a stroke, but, despite his hemiparesis, insisted that he was ready to go home and go back to work. His belief in his ability to walk led to near falls, and he was more interested in sharing this information with the nurses’ station for closer observation. He told the nurses that someone else’s arm was in his bed. On one occasion, holding up his left arm with his right, he told the nurse to, “take it away; it keeps scratching me.” That the left arm “smelled funny” was another reason he wanted the nurses to take it away.

Four weeks after the stroke he first acknowledged that his left arm belonged to him, but never spontaneously recalled being able to move it otherwise. By this time he had a moderate hemiplegia and recognised “a little weak-
ness,” but continued to insist that he was well and able to return to work. By the 6th week and in response to patient more consistently acknowledged that he was weak on the left side of his body. A request for disabled hous-
ing “so that I won’t be a burden to my family” seemed to indicate an appreciation of his impaired function. Slow walking was present; within an hour of making such statements the patient might insist that after a week’s exercise he would be ready to return to work. His awareness of his hemiplegia fluctuated for 8 weeks after stroke before becoming fixed, but remained shallow after 12 weeks; he no longer planned to return to work and applied for social security disability insurance “because they say I’m disabled.” The patient’s mood was remarkably cheer-
ful and optimistic. A week after the stroke he was noted to praise extravagantly the hospital food, and the nurses found him “talkative.” When he arrived on our ward 11 days after the stroke he was in a state of confusion with feverish staff and boasted of having fathered 64 children. His girlfriend was surprised when he kissed her in front of the staff because he had never previously shown affection before. He re-
ported excellent energy and expansively invited all of the staff to his home for thank-
giving. Sleep was not disrupted or reduced and he had a good appetite. When beginning to acknowledge his left sided weakness, he remained blissfully unconcerned. He scored 31 points on a mania rating scale,1 which was well in the manic range. The mania resolved gradually over a 10 week period after stroke. Right sided alcoholism, the patient had no history of psychiatric illness and there was no family history of psychiatric illness. The patient had not seen an physician in many years. Visual acuity was found to be reduced to 20/60 with one eye on the basis of hyper-
tensive retinopathy.

Evaluation 1 month after stroke showed many deficits and a few strengths. Inattention to the left hemipase was marked. By 2 months after stroke he no longer extinguished to double simultaneous stimulation, but, although he could see to the left, was still missing targets in his left visual hemifield. Visual integration, both with and without the requirement of construction, was severely impaired. He was able to correctly recognise and produce facial emotional information. Simple attention was intact, but attentional control (backward span and mental control) was impaired. Visuomotor tracking was slow and he had significant problems with conceptual shifting (with and without visual). Lack of
guage processing difficulties included very poor reading ability, impaired confrontation naming, and impaired performance on a verbal task of fluency and initiation. Auditory comprehension was mildly impaired. Ver-
baculary scored formally in the borderline impaired range, as did abstract verbal reasoning.

On tests of praxis he demonstrated a ten-
dency to use the hand as object. Memory performances were relatively intact. His initial recall of two paragraphs scored for-

mally within the low average range and after a 30 minute delay, he was able to recall most of the information initially encoded, scoring formally within the average range. Structural brain MRI on admission to the emergency room showed a large right thala-
mic hemorrhage with mass effect and oedema, with oedema extending into the cer-

ebral peduncles. Sensory examination was consistent with deoxohaemoglobin. Also present was increased T2 signal bilaterally in frontal areas consistent with ischaemic changes. Brain CT 30 days after stroke showed, in the same structural patterns, moderate cerebellar atrophy and mild to moderate prominence of the frontal cortical sulci compatible with cerebro atrophic. Structural MRI performed 44 days after the stroke showed a 2 cm area of absent thalamic hae-
matoma. Functional MRI performed the same day demonstrated a 2 cm area of absent cerebral blood volume at the posterior margin of the right thalamus without any evi-
dence of decreased cortical blood volume within the right parietal, frontal, or temporal cortex.

This is a case of anosognosia of hemiplegia and mania co-occurring in a patient with a large right thalamic haemorrhage. Although anosognosia and mania are not generally thought of as occurring together, when Babinski’s introduced the term anosognosia he did so on the basis of his experience in a case in which the patient, though not confabulated, was “a little overexcited,” and in a later paper he pre-
sented a case in which there was “a certain agitation, which expresses itself by exagger-
ated loquacity, a decrease in attention, and a tendency to erotic ideas.” Weinstein and Kahn2 noted that euphoria was common in patients with anosognosia. Moreover, al-
though Cutting3 emphasised that apathy is the mood most usually associated with anosognosia, 10% of his patients with ano-
sognosia were described as having “euphoric mood.” Right sided thalamic lesions are known to produce both anosognosia and mania, but the relation of each to the pathology is unclear. Only some of the patients with right hemi-
spheric lesions are manic or agnosic. These two syndromes may be related to dysfunction of different neural networks and only occur together when a disease process affects both networks.

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

Several explanations have been proposed to explain the phenomenon of anosognosia. All the models invoke dysfunction of the cere-


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

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Epileptic cardiac asystole

A patient is reported on with habitual episodes of collapse and loss of consciousness associated with EEG evidence of focal epileptiform discharges. Simultaneous ECG recordings disclosed 25 seconds of cardiac ventricular asystole occurring 24 seconds after the onset of generalised seizure activity. After changes to antiepileptic medication and the insertion of a permanent cardiac pace-

maker he has had no further episodes. In cases of epileptic cardiac dysrhythmia, iso-

lated EEG or ECG recordings may prove insufficient and prolonged simultaneous ECG/EEG monitoring may be required.

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

A previously well 34 year old right handed builder was referred with a 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 reestablished. 16 Channel ictal EEG (eight channels illustrated with ECG) showing electrographic seizure onset and subsequent bradycardia and asystole.
restored and he found himself lying on the floor. On recovery there was no confusion, drowsiness, dysphasia, or diuresis. Often, however, he sustained soft tissue injuries to his face and scalp.

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

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

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

Cardiovascular and neurological examination was normal as were MRI and routine interictal EEG. Sixteen channel ambulatory EEG using an Oxford Instruments digital EEG receiver was performed continuously for 340 hours before an episode was captured. Interictally rare spikes were seen over the right frontocentrotemporal region during sleep. The onset of the episode was not witnessed and the patient was found lying on the floor, regaining consciousness at about 07:06. The event EEG showed a short run of bilateral semirhythmic 2–3 Hz activity at 07:04:34 (figure A), persisting for 8 seconds before being obscured by muscle and movement artefact. Twenty four seconds later, 8 seconds after the brief period of EEG bradycardia, followed by a period of asystole with only very occasional ventricular complexes lasting 8–10 seconds (figure B), there occurred a few seconds of bradycardia then tachycardia, sinus rhythm was restored. Throughout the episode the QT interval on the ECG remained within normal limits. The EEG became visible within normal limits. The ECG showed a short run of bilateral semirhythmic 2–3 Hz activity at <1–2 Hz which persisted for 10 seconds (figure B). This was followed by marked attenuation of the EEG activity over the next 10 seconds before large amplitude generalised rhythmic <1Hz activity became apparent. Diffuse theta activity was seen for a further 15 seconds before the EEG returned to its resting state.

A VVI permanent pacemaker was inserted. The phenytoin was withdrawn and replaced by lamotrigine. Carbamazepine was left unchanged. The patient was discharged, his medication left unaltered, and at follow up 9 months later reported no further episodes.

Cardiac dysrhythmias are an uncommon but serious consequence of partial seizures. Our case is unusual because of the duration of the episode and a series of 26 patients with 74 temporal lobe seizures in which simultaneous EEG and ECG recordings were acquired, ictal arrhythmias occurred in 52% of seizures, the commonest being irregular abrupt changes in heart rate, (both acceleration and deceleration) occurring towards the end of the period of EEG abnormality. Interictally, patients with epilepsy seem no more likely than age and sex matched healthy subjects to experience arrhythmias although in one study patients with epilepsy had a faster ventricular rate and a longer QT interval than controls.1

It has been hypothesised that there is lateralisation with respect to central autonomic cardiac control with an increase in heart rate seen after an increase in generation of amobarbital and inactivation of the left hemisphere and a decrease in heart rate on right hemisphere inactivation. Experimental stimulation of the rostral posterior insular cortex in anaesthetised rats has been shown to induce tachycardia and more caudal region stimulation to cause bradycardia.2 Addition ally, prolonged stimulation resulted in ventricular ectopies, heart block, QT prolongation, and death. In preclinical temporal lobectomy patients stimulation of the left insular cortex (particularly posteriorly) produced bradycardia and a depressor response significantly more often than tachycardia and a pressor effect. It was suggested that an epileptic discharge in the insular cortex may result in cardiac arrhythmias. Recurrent episodes of loss of consciousness are a common clinical problem. An accurate diagnosis relies principally on the patient's and witnesses' accounts of events. Further investigations are frequently required which are often normal unless an episode is captured during monitoring. Recording solely the 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 1.5 Mb deletion in chromosome 17p11.2 including the peripheral myelin protein-22 (PMP-22) gene. HNPP typically presents recurrent pressure palsies of peripheral nerves, such as the axillary, median, radial, ulnar, or peroneal nerves, at common entrapment sites. Respiratory muscle weakness has not been previously reported in HNPP. We describe a patient with HNPP whose respiratory failure and proximal muscle weakness were prominent features.

The patient started to have dyspnoea on exertion at the age of 44. At the age of 47, he noticed a slowly progressive weakness of the pelvic girdle and lower limbs. At the age of 57, he experienced difficulty in going up stairs. However, he was almost independent in daily life. At the age of 60, he was admitted to St Mary Red Cross Hospital with a coma due to CO2 narcosis (PCO2, 117.6; PO2, 64.0). Responsive to mechanical ventilatory support, he completely recovered consciousness within a day.

In a neurological examination, the patient's mental state and cranial nerves were normal. Evidence of muscular atrophy was absent. Proximal weakness of both lower limbs 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 reflexes were present in all four limbs (figure). There was no evidence of deep tendon reflexes. There was no spasticity. The patient had normal results. No monoclonal or polyclonal antibodies to gangliosides GM1 and GD1b were negative. Analysis of CSF showed 1 lymphocyte/mm3 and 25 mg/dl protein. Motor nerve conduction studies showed prolonged distal latencies in the right median (8.8 ms (normal value in our laboratory <4.6)) and ulnar (6.2 ms (normal<3.6)) nerves, and moderate decreased conduction velocities in the right median (nerves (normal>45)), ulnar (45 ms (normal>49)), tibial (35 ms (normal>38)), and peroneal (29 ms (normal>41)) nerves. There were moderate decreases in the amplitude of compound action potentials in all the nerves tested, and an amplitude reduction of 50% was detected across the cubital tunnel of the right ulnar nerve. Minimum F wave latencies were prolonged in all the nerves tested. The latency in the right phrenic nerve was slightly decreased. The response to the stimulus was absent in the right median nerve at the wrist, suggesting a complete lesion of the median nerve in the distal arm. The response to the median nerve at the wrist was normal.

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of myelinated fibres was reduced (5726/mm²). Sensory nerve conduction studies showed a reduced amplitude of sensory nerve action potentials and conduction slowing in all the nerves tested. Electromyography carried out in the supraspinatus, deltoid, biceps, flexor carpi ulnaris, brachioradialis, quadriceps femoris, biceps femoris, tibialis anterior, and gastrocnemius muscles showed polyphasic motor unit potentials of long duration, but denervation potentials were rare. A left sural nerve biopsy showed scattered tomacular thickening of the myelin sheath and some abnormal myelin sheaths. The density of myelinated fibres was reduced (5726/mm²). A gene analysis disclosed a 53% gene dose of PMP-22 related to normal controls, using Southern blots of DNA digested with EcoRI.

Given the possibility of superimposing demyelinating neuropathy, especially chronic inflammatory demyelinating polyneuropathy, oral prednisolone (60 mg/day) was given for 1 month. However, the patient’s clinical condition did not respond to this treatment. Pulmonary dysfunction and proximal muscle weakness were almost steady during the next 3 years.

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

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

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

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

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

Spinal accessory neuropathy and internal jugular thrombosis after carotid endarterectomy

Spinal accessory neuropathy is a rare complication of carotid endarterectomy (CEA). Internal jugular venous thrombosis after CEA has also been reported rarely, but is likely more common; as internal jugular...
venous thrombosis is often asymptomatic, or presents with non-specific pain, it is probably underrecognised in many cases.1 Concerted ipsilateral spinal accessory neuropathy and internal jugular venous thrombosis after CEA is expected to be rare, and this is underscored by the small number of reported cases. Despite this apparent rarity, a common pathogenetic mechanism for postoperative spinal accessory neuropathy and internal jugular venous thrombosis may well be present, at least in some cases, which may lead to the consideration of the possibility of both when either is discovered.

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

The cause of spinal accessory neuropathy was not determined. Weary 1 year after CEA first reported as a complication of CEA in 1982.1 Since then, there have been several case reports and small series.2 A 1996 review of reports of cranial neuropathy after CEA disclosed only one patient with spinal accessory neuropathy in over 3000 cases.3 Although the authors did not include several other reports4 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 CEsAs that have been done worldwide suggests that clinically significant spinal accessory neuropathy is a rare complication. Minor spinal accessory neuropathy after CEA may be more frequent. The cause of spinal accessory neuropathy after CEA is usually not well established, but intraoperative nerve stretching or compression from retraction is most often invoked.5 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.6

The spinal accessory nerve courses along the internal jugular vein and near the internal carotid artery, typically well above the carotid bifurcation. This should mean 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 remains to be seen.

From our search, internal jugular venous thrombosis after CEA has been reported in only one case.2 As Southcott et al noted, retraction of the internal jugular during CEA may cause complete occlusion, 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 several centimeters after neck dissection, often with recanalisation after several months.6

The presence of induration about the incision site and a palpable supraclavicular cord in our patient led us to suspect venous thrombosis. Internal jugular venous thrombosis may often be asymptomatic. Potential symptoms of internal jugular venous thrombosis include headache, dysphagia, and anterolateral neck pain, tenderness, and swelling. In addition to perivenous induration, fever and leukocytosis may occur.7

Common pathogenetic mechanisms for spinal accessory neuropathy and internal jugular venous thrombosis may include intraoperative traction, haematomata, and postoperative inflammation and scarring. Although the onset of either spinal accessory neuropathy or internal jugular venous thrombosis in our patient cannot be determined precisely, it is likely that both developed at about the same time. The delayed worsening of 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 alert the medical 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 1996. 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 arterial infarct. Cervical ultrasound duplex scanning and cerebral angiography were normal. Cerebral CSF examination was normal except for a patent foramen ovale.

The patient had no vascular risk factors, in particular no tobacco use, and he was perfectly fit until his stroke. He was a sportsman with 2 hours daily intensive training for body building. He was working as a baggage handler in an international airline company. During a recent journey to Miami, Florida, he bought tablets of “energy pills” in a shopping 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 caffeine, and 6000 mg creatine monohydrate daily for about 6 weeks before his stroke.

Although a paradoxical embolism through a patent foramen ovale in this patient cannot be ruled out as he recently underwent transatlantic air flight, there was no deep venous thrombosis and D-dimers were normal. However, ephedrine has an indirect sympathomimetic action and may promote arteriovenous constriction in addition to other catecholaminergic effects. Both ischaemic and haemorrhagic stroke associated with ephedrine use have been reported.8 Acute myocardial infarction and acute psychosis have also been reported after taking ephedrine and other sympathomimetic drugs.9 Ephedrine and its metabolites are natural products that are used in non-prescription medicines for multiple uses. Ephedra extract (corresponding to 20 mg ephedra alkaloids) is a common ingredient in some energy drinks. Ephedrine contains ephedrine, which is a sympathomimetic amine, and 6000 mg creatine monohydrate daily for about 6 weeks before his stroke.


it remained in the normal range. Whether the use of high doses of caffeine can enhance the cardiovascular effect of ephedrine remains a possibility as stroke after taking a combination of caffeine and amphetamine has been reported.1

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

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

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Petroclival meningioma as a cause of ipsilateral cervicofacial dyskinesias

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

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

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

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

An MRI study showed a large gadolinium enhancing tumour within the left cerebellar hemisphere extending to the cistern magna 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 meningeomas. The tumour was totally removed by a combination of transpetrosal supratentorial and infratentorial presigmoidal approach. The postoperative course was uneventful and there were no new deficits. The facial palsy improved slightly as well as the trigeminal hypaesthesia. Audiometry remained unchanged. Postoperative imaging showed no residual tumour and the displacement of the brain stem within the posterior fossa had resolved (figure C). Marked improvement of the left sided craniofacial dyskinesias occurred during the next weeks.

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

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.1 This case provides further evidence that functional impairment by compression and distortion of the brain stem may cause hyperkinetic cerebellocerebral 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 a surgically treatable cause.

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Acute multifocal cerebral white matter lesions during transfer factor therapy

Transfer factor is an active substance of unknown structure present in dialysable leucocyte extract which is assumed to transfer cell mediated immunity in an antigen specific fashion.1 The mechanisms of action of transfer factor are still far from clear; in vitro dialysable leucocyte extract increases macrophage activation and interleukin (IL) 1 production and enhances leucocyte chemotaxis and natural killer function. Transfer factor has been reported to stimulate the cell mediated antigen specific response in patients with various infections1; therefore, treatment with transfer factor has been suggested in patients with selective deficits in cell mediated immunity due to some refractory neoplasms and chronic infections. Moreover, it has been used in the treatment of uveitis.1 Administration of dialysable leucocyte extract has seemed to be free of hypersensitivity, long lasting side effects, or complications, except for transitory hyperpyrexia.1

We report on a patient in whom multiple cerebral white matter lesions developed after taking dialysable leucocyte 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 reflux of the right eye. In January 1995 retinal vasculitis was diagnosed at fundoscopy and in July 1995 he started oral transfer factor as dialysable leucocyte extract twice a week. He complained of generalised weakness after the second dose and the referring symptoms developed after the third dose.

Neurological examination on admission showed mental confusion and severe right spastic hemiparesis with right 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, antitryptosin titles (355 UI/ml, normal <200 UI/ml), and anticardiolipin IgG (30 UI/ml, normal ≤12 UI/ml). Negative results were obtained for HIV, hepatitis virus B and C infection were not IgM against cytomegalovirus (CMV), Herpes simplex, Varicella zoster, Epstein-Barr virus, Toxoplasma gondii, the Paul Bunnel reaction, anti-HIV, and the markers of hepatitis virus B and C infection were negative.

Cell, protein, and glucose concentrations in CSF were normal. No oligoclonal bands or antibody against CMV, Herpes simplex, Varicella zoster, Epstein-Barr virus, Hepatitis virus A, B, and JC virus in the CSF was negative.

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

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

The close temporal relation between assumption of dialysable leucocyte extract therapy and appearance of cerebral white matter lesions in our patient supports the hypothesis 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-Behçet's disease although in the absence of biopsy. In fact, the clinical, laboratory, and MRI findings were not typical and a low titre of anticardiolipin antibodies is found in 2% of healthy subjects.

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

The pathogenic mechanisms underlying the triggering, development, and duration of multiple sclerosis and acute disseminated encephalitis are still far from clear despite the progress made in unravelling them. Some findings suggest that acute disseminated encephalitis and multiple sclerosis lie at the same time of focal cerebral white matter lesions highly supports the diagnosis of multiple sclerosis. On the other hand the possibility that acute disseminated encephalitis may recur has been accepted and on the basis of the patient's clinical picture and CSF, we favoured such a diagnosis.

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

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

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

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

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

Neurological examination showed bilateral hyperreflexia, mild impression of fine finger movements, dysgraph aesthesia on sensory testing, and a maneristic gripping handshake. There were no extrapyramidal features such as a hypertonia or rigidity. In the left arm, the hypertonia was associated with tremor and possible myokymic phenomena. In the right arm, tremor and myokymia were not seen. In contrast, the lower limbs were hypotonic and displayed a moderately delayed gait. He had mild pyramidal and extrapyramidal signs, including a resting tremor of the right hand, as well as a slow, alternating, and cerebellar coordination on the right hand. His speech was slow and monotonous with a high pitch. Auditory comprehension was normal. He displayed signs of an impaired abstraction ability and of a poor memory. He was able to solve simple arithmetic calculations, but was unable to perform more complex calculations, and had problems with spatial orientation. He was able to draw a house, a wheel, and a bicycle, but was unable to draw a human figure. He was unable to explain his drawings and was not able to do the tasks.

The neurological examination also revealed multifocal brain calcifications.

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

Brain CT showed dense calcium deposits in the basal ganglia, thalamus, cerebellar dentate nucleus, and orbitofrontal cortex, consistent with Fahr’s disease (figure). SPECT showed increased activity in basal ganglia relative to the cerebral cortex. A fine-tuned dopamine-dopamine metabolism could produce an autistic syndrome when brain calcifications cause specific neurological deficits, due to their localisation. For example, errors of social judgement may be related to calcifications of the orbitofrontal cortex, whereas dysfunction of frontal-basal ganglia circuits may contribute to repetitive and ritualistic activities. Additionally, developmental lesions of the basal ganglia and cerebellum may contribute to the abnormalities of sensory attention, procedural learning, and motor intention in this patient.

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

Preoperative sagittal T1 weighted MRI of the cervical spine with gadolinium enhancement. A retroodontoid and extradural mass displacing the spinal cord is seen at the craniovertebral junction.
Selective hemihypesthesia due to tentorial coup injury against dorsolateral midbrain: potential cause of sensory impairment after closed head injury

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

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

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

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

T2 weighted images 1 month later showed a more localised lesion in the same area. The coronal slices showed a high intensity lesion at the level of lower midbrain coinciding with the tentorium level, disclosed as a low line between the occipital lobe and the cerebellar hemisphere (figure).

The neurological deficits almost disappeared 6 months later.

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

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

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

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

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We read with interest the article by Miyagi et al and comment on the medical treatment of tolune induced tremor. Microdialysis experiments in rats have shown that inhalation of tolune increases extracellular γ-amino butyric acid (GABA) concentrations within the cerebellar cortex which probably explains why GABA agonists including benzodiazepines (for example, clonazepam) are not very effective in tolune induced tremor and ataxia. Rat experiments also showed a 50% reduction in brain catecholaminergic neurons. The degeneration of certain cerebellar pathways is probably responsible for the loss of this dopaminergic innervation. Dopamine agonists could therefore be of potential interest in the treatment of tolune induced tremor. This hypothesis was explored in a recently described case, which showed remarkable clinical and imagongraphic similarities with that described by Miyagi et al: (a) long history of chronic tolune inhalation, (b) marked postural tremor, (c) progressive worsening of the symptoms after abstinence from inhalant misuse, and (d) mild cerebellar 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 previously been shown to be helpful in the treatment of parkinsonian symptoms and has been shown to be effective in the treatment of sporadic and hereditary forms of extrapyramidal disorders. In addition, there is evidence that catecholaminergic pathways are also involved in this type of ataxias, supported by loss of pigmentation of these neurotransmitters in the CSF of patients with hereditary extrapyramidal disorders in which the dopaminergic innervation is absent. In addition, there is evidence that catecholaminergic pathways are also involved in this type of ataxias, supported by loss of pigmentation of these neurotransmitters in the CSF of patients with hereditary extrapyramidal disorders in which the dopaminergic innervation is absent. In our patient, amantadine hydrochloride (100 mg twice daily) abolished postural tremor and ataxia completely over a 3 month period.

Subsequently, the treatment was discontinued, which resulted in relapse of the tremor and ataxia. He was rechallenged to amantadine hydrochloride (100 mg twice daily) and this abolished the symptoms completely over a 3 month period. 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 tolune induced tremor and ataxia. Intractable cases would then justify a more aggressive approach such as ventroummedullary thalamotomy.
“man-in-the-barrel” syndrome has even been suggested. Probably all these terms used to define this variation of ALS are synonyms for an older, well known condition, the scapulopelvic form, or the chronic anterior poliomiyelitis reported by Vulpian in 1886 and known in Franco-German literature as Vulpian-Bernhardt’s form of ALS. At certain stages of the disease’s clinical course, it is probably difficult to differentiate it from progressive muscular atrophy (PMA). Some authors have said that PMA with late onset scapulopelvic distribution (over 45 years of age) generally leads to ALS as a matter of course.1 Be that as it may, the truth is that this atypical form of amyotrophic lateral sclerosis behaves differently from typical ALS. The comparative study with the rest of the ALS group supplied important clinical findings, such as little or no functional impairment of the bulbar muscles or legs. Hu et al.2 also made four important statistical discoveries.

(1) The prevalence of this form of ALS constituted 10% of the ALS group as a whole (p=0.57). The age of onset of this form was similar to the rest of ALS. (3) There was a clear predominance among men (the male/female ratio was 9:1 in this form, compared with 1.5:1 in the total ALS group). (4) There was a longer median survival (a median survival of 57 months compared with 39 months in the ALS group).

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

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

We do not know the reason for either the characteristic distribution of weakness or muscle atrophy. A meticulous study shows that there is an atrophy of the deltoid, quadriceps, and iliopsoas muscles (ipsilateral to the palsy spinata) 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 presence 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 presence of progressive deterioration of the symptoms, the appearance of bulbar signs, and the absence of sensory symptoms and signs would favour the diagnosis of ALS.3


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. As in their patients transcerebral magnetic stimulation induced absent or delayed corticofugal responses at the tongue, the authors ascribed isolated dysarthria to interruption of the corticobulbar pathway, involving the thalamocortical and corticostriatal fibres as well as the corticothalamic fibres. In fact, lacunar infarctions around the internal capsule-corona radiata are likely to underlie these ascending and descending pathways.

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. As in their patients transcerebral magnetic stimulation induced absent or delayed corticofugal responses at the tongue, the authors ascribed isolated dysarthria to interruption of the corticobulbar pathway, involving the thalamocortical and corticostriatal fibres as well as the corticothalamic fibres. In fact, lacunar infarctions around the internal capsule-corona radiata are likely to underlie 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 included that the corticopontocerebellar tract is preserved in isolated dysarthria because of no evidence for cerebellar diaschisis on SPECT. Their SPECT findings on cerebellar blood flow were similar to our results. However, we wonder whether cerebral cortical blood flow was preserved in their patients, because our SPECT study suggested frontal cortical dysfunction as an underlying mechanism of isolated dysarthria. Langugage impairment is 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 formulation as well as a language paradoxa.

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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 choreatic dyskinesias. Chorea itself is often reduced in the more advanced Huntington’s disease stages. It is unlikely, therefore, that any norephophysiological 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.

We were not really surprised at the results of Hanajima et al as we do share their opinion that patients with Huntington’s disease may be characterised by large individual differences in the involvement of motor cortical areas. Actually, three patients in our study showed an amount of intracortical inhibition within the confidence limits of the control population. We also think that the impairment of intracortical inhibition is likely to develop during the 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 4.4 mV compared with 0.5 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 also1) than in the study of Hanajima et al.

When interpreting the results of studies with paired transcranial magnetic stimulation pathophysiologically it should be kept in mind that similar changes of intracortical inhibition have been shown in patients with various movement disorders (focal dystonia, myoclonus, parkinsonism, restless legs syndrome, Tourette’s disorder), but also in different diseases such as amyotrophic lateral sclerosis. We, therefore, believe, 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.

Motocortical 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 may be due to differences in patient selection as they included patients with early stage Huntington’s disease to “study the pathophysiology of chorea unaffected by other movement disorders.” 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 discrepancy between the two studies may be mainly due to the different stage of the disease between the two groups of patients. Although the duration of the disease is one factor to judge the disease stage, the severity of the disease (stage of the disease) is also positively correlated with CAG repeat number.

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

We also consider that methodological differences are very important in paired magnetic stimulation. The results strongly depend on the intensities of both a conditioning and a test stimulus. Especially, the intensity of the conditioning stimulus is critical. We have no difficulty in showing normal inhibition, but have much difficulty in showing reduced or absent inhibition because of such marked dependence of the results on the intensities of stimuli. Therefore, we used a range of intensities of the conditioning stimulus before we confirmed inhibition in studies of patients. We used an intensity of 5% less than the active threshold as a conditioning stimulus, a facilitatory effect must often superimpose on the intracortical inhibition. This makes the interpretation difficult. Was the intensity of 80% of the resting threshold below the active threshold in their patients? In our experience, 80% of the resting threshold was sometimes above the active threshold. These factors must be considered in interpreting the results of paired magnetic stimulation.

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

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

\[ FV(t) = (ABP(t) - CCP) / CVR \]  

(1)

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

\[ FV(t) = (ABP(t) - CCP) / CVR \]  

(2)

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

CCP2=ABP−A1/F1=FV  

(4)

leads to 

CCP2=ABP−CVR1/CVR0×(ABP−CCP) =ABP−CVR1/CVR0=FV  

(5)

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

CCP2=0.5ABP×0.5CCP  

6

With decreasing CVR1/CCR0 ratios, CCP2 becomes more and more independent on ABP and independent of CCP. In any case, without exact knowledge of the CVR1/CCR0 ratio, equation 4 is useless for a valid CCP calculation.

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

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

Finally, I would be interested in the authors’ explanation of negative diastolic flow values as seen in Dopper 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 zero 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 FV is more accurately given by cerebral perfusion pressure (CPP=ABP−ICP) than by ABP−CPP. Therefore, equation 2 changes to 

\[ FV(t) = (ABP(t) - ICP) / CVR0 \]  

(6)

and equation 5 to 

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

(7)

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

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Czosnyka et al reply:

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

CCP=ICP+active tension of arterial walls

Aaslid proposed the mathematical formula taken for calculations:

\[ CCP=ABP−ABPpp+FFVp×FFV\]  

(8)

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

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

\[ CCP=ABP−A1×FV \]  

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

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

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

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

The final issue concerning negative flow velocities is a trap Diehl has prepared for himself. We never suggested that any factor interpretable as cerebrovascular resistance (CVR0 or CVR1) should be involved in the concept of critical closing pressure. From the definition, closing is a strongly non-linear phenomenon, therefore applying linear theory here is very
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thalamic nucleus
pallidum internum may be as relevant.

associated with chorea-ballism in monkeys.

encoded proportions describing properties of the
cerebrovascular bed. Whether it simplifies our
knowledge—we personally find it doubtful.

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

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

Reduction in the neuronal activity of the sub-
thalamic nucleus leading to diminished exci-
tation of the globus pallidum internus is associa-
ted with chorea-ballism in monkeys.2 Levodopa induced dyskinesias are currently thought to share a similar pathophysiology3 but recent findings also suggest that abnor-
mal patterns of neuronal firing in the globus
pallidum internum may be relevant.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 Figueiras-Mendez et al.7 Ideally we would like to see the trajectory and length of the differ-
ent recording tracks, the effects of micro-
stimulation, 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.

Figueras-Mendez et al reply

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

Recognition of the electrical activity of the subthalamic nucleus has been facilitated by the follow-
ing criteria: (a) high frequency discharge (25 Hz or higher) within the nucleus;8 (b) a tonic (regular), phasic (irregular) or a rhythmic pat-
tern of discharge; (c) response to voluntary/ passive movements.8 When rhythmic dis-
charges were recorded irregular passive manipulations were performed or the patients asked to move the limbs irregularly; (d) response to tremor activity. Positive cells were so considered based on correlation of the EMG with the accelerometer re-
corded simultaneously. Artificial manual stop-
ning by one experimenter (confirmed by visual inspection, silence in the EMG, and stoppage in the oscillating accelerometer) and/or spontaneous arrest in the tremor modified the firing frequency and discharge pattern or rhythmic cells corroborating the tremor nature of the cells; (e) the activity of these cells above the subthalamic nucleus. A lower background noise level; (f) the activity of substantia nigra pars reticulata cells when further lowering the microelec-
trode. These cells discharge at high frequency at regular intervals as identified in patients’
and primates.7 All these points were fulfilled by the patient reported.

Considering the questions in the letter by Obeso et al, we make the following com-
ments: (a) Action potentials of large amplitudes less than 0.3 mV and could not be
considered large amplitude potentials. We start to record activity from 3 mm before
to enter the subthalamic nucleus, traverse the length of the subthalamic nucleus, and go
farther down several mm to encounter the substantia nigra pars reticulata cells. Changes in
the background activity are clearly recog-
nised and are higher when entering the subthalamic nucleus. Enough cells are re-
corded along the tracks experimentally to recognise a large amplitude potential.
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.11 In our report, cells discharged tonically, but also other cells fired phasically, well differentiated by a profuse burst activity and identified by statistical means (autocorrelation and interval histograms). (b) Motor responses and tremorgenic cells in line with the above mentioned criteria were found along the trajectory of the electrode. Unfortunately, this point was not mentioned in the paper. It would surely have changed the opinion of Obeso et al.

In the contralateral patient, a total of eight neurons were recognised as belonging to the subthalamic nucleus in the right hemisphere, with a mean frequency of 74 Hz (range 38–109 Hz). Four of them responded to voluntary movements of the right hand and, only when the symptoms are considered, tremolinex was also positive to tremor. The stimulating electrode was placed in laterality 11. The activity of the cells recorded. In the other track, nine neurons were recorded in the subthalamic nucleus (always following the above mentioned criteria) with a mean of 69 Hz (range 17–98 Hz). Five cells responded to passive and/or voluntary movements. One of them was also positive to tremor. The stimulating electrode was placed in laterality 12. The mean background stimulating electrode is always tested in the surgery before cementing it and, only when the symptoms are considered of unquestionable benefit it is left in the chosen place. The final position of the electrodes, assessed by ventriculography, was as follows: (a) posteroanteriort: 1.5 mm behind the mean point of intercommissural line, (b) height: 6–6.5 mm below the intercommissural line, and (c) lateral: 12 mm for the right hemisphere, and 11.5 mm for the left hemisphere.

**NITRIC OXIDE IN ACUTE ISCHAEMIC STROKE**

The pivotal role of nitric oxide (NO) in cerebral ischaemia has been elegantly highlighted in the recent editorial by O’Mahony and Kendall.1 Although studies of neuroprotective agents have been largely disappointing, pharmacological manipulation of NO may represent a novel means of protecting the brain from ischaemic insult. One area not discussed in the recent reviews is the neuroprotective effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or “statins” in cerebral ischaemia. Preliminary studies have shown that statins modulate brain nitric oxide synthase (NOS) activity in a neuroprotective manner. Data from a murine model of ischaemic stroke demonstrate that prophylactic statin therapy reduces infarct size by about 30%, and improves neurological outcome in normocholesterolaemic animals.16 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 manipulates the ratio 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 new class of anti-inflammatory responses that accompany ischaemia. Most interestingly, these preliminary findings suggest that statin therapy may modify the mitochondrial few faces of brain NO in a synergistically neuroprotective manner. These and other vascular effects1 of statins in cerebral ischaemia are potentially of great importance in human neuroprotection and ongoing research explores the The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study17 will help clarify their role in human cerebrovascular disease.

**BOOK REVIEWS**


That neuroinflammation has come of age is demonstrated by the profusion of volumes published in the subject in recent years. This volume focuses on the central nervous system, and aims to satisfy the curiosity of both the effcacious clinician faced with a diagnostic conundrum and the experimental immunologist inquiring into the clinical relevance of his findings. At first sight it seems improbable that both of these goals might be achieved in one volume; this book however, succeeds admirably in what it sets out to do, as much as a result of its literary style as its content. The intrusive authorial voice fell into disfavour in literary circles around the turn of the century because it was thought that calling attention to the act of narrating might detract from realistic illusion, so reducing the emotional intensity of what was being represented. It is a device much favoured by postmodernists, 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 immunology of the nervous system. There follows a chapter that integrates the neurobiology of multiple sclerosis with contemporary issues of aetiology, cell injury, and repair. Next, a chapter on inflammatory demyelinating diseases examines syndromes of isolated demyelination, acute disseminated encephalomyelitis and allied conditions, and some of the syndromes of demyelination that are now accepted as part of the range of multiple sclerosis. The chapters on demyelinating disease are drawn to a close by a discussion of existing and experimental therapies for multiple sclerosis. The book continues with chapters on paraneoplastic disorders of the CNS, stiff man syndrome, neurological complications of...

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 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 minimal 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 ontogenetic models in the understanding of the management of Alzheimer's disease particularly interesting. However, the papers of original research are of more limited interest to the general reader. Although, as mentioned, the quality of illustrations is good, there is some variability in the definition of abbreviations and occasional lapses into other European languages.

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

JON SUSSMAN


Organ transplantation, once medical exotica, is now almost commonplace. In the United Kingdom each year are performed cadaveric organ transplants of about 1800 kidneys (in addition to 160 live kidney donors), 700 livers, and 450 heart/lungs (UK Transplant Support Services). In basic surgical technical techniques were established at the beginning of the century in canine models. Transplantation of these experiments to humans awaited safe and effective immunosuppression. Until the 1960s, the only forms of immunosuppression were radiation (total body or total lymphoid) and non-selective chemical reagents (benzene and tolenu). The antiproliferative drug 6-mercaptopurine (6-MP) was introduced, shortly followed by a derivative, azathioprine, with improved oral bioavailability. Combined with corticosteroids, these allowed the first human solid organ transplants to be performed: in 1964 the first lung transplant in Mississippi and liver transplant in Colorado. Then in 1967 Christian Barnard captured the world's imagination with the first heart transplant. His technique has been modified slightly since, but the increasing success of organ transplantation rests mainly on improved immunosuppression with drugs that selectively suppress lymphocytes by inhibiting lymphokine generation (cyclosporin A, tacrolimus), renal transduction (sirolimus, leflunomide), or differentiation (15-deoxyspergualin) pathways. As a result, over the last 10 years in the United Kingdom, the 1 year survival of grafts has improved from 80% to 90% (kidney), 55% to 75% (liver), and 70% to 90% (heart/lung).

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

CLARE GALTON


Volume nine of the Current Issues in Neurodegenerative Disease series examines the interplay between cerebrovascular disease and dementia, particularly Alzheimer's disease. Two hundred pages of what are essentially 20 brief review articles comprise this text, sadly without any illustrations. Perhaps some common genetic factors are responsible and here the apoE alleles are discussed. The comprehensive section on deep white matter lesions seeks to explain the connection further—and convinces the reader that there is still a lot which is not well understood. It is in this section particularly that illustrations are greatly missed. Brief mention is made of other conditions which may produce white matter changes and dementia such as CADASIL, cerebral lupus, and the primary antiphospholipid syndrome.

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

PETER MARTIN


Evolutionary biologists would probably tell us that the enchantment of stories is due to survival having been dependent on the passing of oral culture from one generation to the next. Information put in narrative form not only delights, but is easily recalled. Stories also construct the world by involving 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
Holmes.
are two very fine accounts of narrative in psy-
but over worked paradigm. However, there
sters concerning attachment theory, a useful
issues, and there is repetition in various chap-
for all psychiatric trainees.
paper alone, which should be required reading
psychiatric library should buy this book for this
als by their illness as in schizophrenics. Every
patients and professionals of identifying individu-
by their illness as in schizophrenics. Every

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

**DUNCAN MCLEAN**


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

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

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

**LINA NASHEF**


**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 their parents) 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 spe-
cific chapter in view of the unique electro-
clinical evolution and natural history of this syndrome. The crucial issue of the cognitive and behavioural sequelae of early and fre-
quency seizures on the immature brain, which is probably of most concern to both clinicians and families, is succinctly addressed in two chapters—although a clear and consistent cause and effect relation remains to be estab-
lished. The chapters covering basic neuro-
physiology, neurochemistry, and neu-
ropathology, are erudite and fascinating but at times are barely comprehensible. Further
work is needed, including answering the fun-
damental question—why does the first sei-
zure 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 com-
mandable and I expect that 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 an attempt at prolonged editorial atypical absence, and although this militates against it becoming a well thumbed reference text, the book is an erudite addition to the mossy fibre-like sprouting of the epileptologi-
cal literature.

**RICHARD E APPLINGTON**


Difficult clinical problems in psychiatry come in many forms. Diagnosis often causes difficulty, particularly in cases in 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 psychopharma-
cological 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 pharmacologi-
cal 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. Readers will find chapters covering all aspects of the assessment and management of anorexia nervosa and chronic fatigue are followed by a thorough review of the pharmacological management of substance misuse. Then come two weak chapters on behavioural disturbances in old age and the violent patient in the community. This last chapter will be of particular interest to community psychiatrists, a topic that I would recommend because some aspects of the practical management of violence are missing—for example, a documented risk-benefit analysis, good failsafe communication, or deciding when to detain. One of the last chapters is a very good account of the management of hyperactivity in childhood, with good practical advice on the use of meth-
lyphenylate.

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

**SIMON FLEMINGER**


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

The book is divided into sections dealing with the treatment of broad groups of clinical disorders—for example, psychosis—special patient populations—for example, elderly people, with further sections on the manage-
ment of emergencies and the adverse e-
effects of psychotropic drugs. Much of the information is laid out in tabular form. It could become an indispensable resource for a busy on call sen-
tor house officer (the dimensions would fit comfortably into the pocket of a clinical white
coat, were they still to be worn) but more sen-
ior clinicians will find plenty of use for it in the clinic. It does not aim at difficult conditions, 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 psychosis (39 pages). The brevity is only partly explained by the undeveloped state of that particular area of psychopharmacology. Sections on common indications to and contraindica-
tions for lumbosacral puncture and indications for EEG seem to have been displaced from some other primer for busy junior doctors. There is no index.

These quibbles apart, prescribing guide-
lines can be wholeheartedly recommended.

**BRIAN TOONE**