LETTERS TO THE EDITOR

Postictal psychosis related regional cerebral hyperperfusion

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

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 Antiepileptic drugs were withdrawn to facilitate seizure recording.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

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

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

Cerebral SPECT performed during the interictal period (IP) and during postictal psychosis (PP) were analysed visually and areas of hypoperfusion were identified. Quantitative data at regions of interest (ROIs) were measured on coronal and axial slides containing basal ganglia (BG), mesial (MT), and lateral (LT) temporal lobe structures. Asymmetry index (ASI) was calculated as (ROI focus−ROI contralateral)/ROI focus+ROI contralateral)×200%. 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 and PP over right MT was +75% (-6.64-46 to -1.6528); 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 18.76057); and over left BG was +155.9% (-5.85556 to 3.27522).

Postictal psychosis is a distinct clinical event associated with temporal lobe epilepsy.1 The diagnosis of postictal psychosis requires a close temporal relation between bouts of complex partial seizures and the onset of psychosis. The psychosis usually develops after a clinical seizure, or partial seizures were precipitated by abrupt withdrawal of antiepileptic drugs. The cluster occurs in patients with poor drug compliance or during video EEG telemetry studies when antiepileptic drugs are not dose-adjusted. The clinical course of postictal psychosis is usually benign and unpredictable.1 In our patients, the duration of psychotic disturbances lasted from 2 to 7 days, which is in keeping with the good prognosis. Antipsychotic drugs, such as haloperidol and fluphenazine are usually prescribed.1

The underlying mechanism of postictal psychosis is unknown. Postictal cerebral hypofunction has been postulated as an analogue to Todd’s paralysis after seizure.1 However, the presence of increased rCBF during postictal psychosis, may suggest an alternative explanation as ictal SPECT has been shown to be highly sensitive and specific in demonstrating seizure foci.1 To conclude, our results are contradictory to the hypofunction theory of Todd’s paralysis after seizure.1

Oncocelreal matrix glycoproteins in cerebral arteriovenous malformations and neighbouring vessels

Cerebral arteriovenous malformations (AVMs) are thought to be congenital lesions exhibiting features of either mature vascular walls or embryonal anastomotic plexuses. It is generally assumed that changes in size are dependent on enlargement of the venous compartment, organisation in the setting of microhaemorrhages, and gliosis. However, recent findings are consistent with the hypothesis of ongoing angiogenesis.1

Previous research from our laboratory disclosed that peculiar isoforms of fibronectin (FN) and tenasin (TN) typically occur in fetal and neoplastic tissues. These isoforms are a blend of structurally different glycoproteins that result from alternative splicing of the primary transcript and are mainly expressed in the extracellular matrix. Their expression is undetectable in normal adult tissues, with the exception of the vessels in the regenerating nidus, irrespective of their morphology. For the recombinant antibodies BC-1 and TN-12 the recombinant fragment containing the epitope produced in E Coli. For the mAb BC-1 we used the recombinant protein containing the type-III repeats 7B–8–9. For the mAb IST-4 we used the recombinant protein containing the type-III repeats 2–8. For the recombinant antibodies TN-11 and TN-12 the recombinant type-III repeat C and the recombinant fragment containing the EGF-like repeats were used.

All 10 AVMs were found to contain large amounts of FN and TN, as shown by intense immunostaining with the use of the IST-9 / IST-4 mAbs and the TN-12 Ab fragment. The staining was localised either in the endothelium or the subendothelial layer. A positive response was found in several artery-like vessels and in a few vessels with thinner walls using the mAb BC-1. Staining with the TN-11 Ab fragment showed occurrence of type III repeat C TN isofrom 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 angiomatus nidus. In all these cases the wall of several vessels exhibited intense staining with the use of the TN-11 Ab fragment. Using the BC-1 mAb some of these vessels exhibited some staining (figure). In the control specimens (brain and cerebellum) both the FN isoform containing the ED-B sequence (ED-B+FN) and the type III repeat C TN isoform were absent, despite the widespread distribution of total FN and TN in the vascular walls.

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

<table>
<thead>
<tr>
<th>Anti-FN mAbs1</th>
<th>Anti-TN Ab fragments4</th>
<th>Total TN</th>
<th>Type III repeat C Isoform</th>
</tr>
</thead>
<tbody>
<tr>
<td>IST-4</td>
<td>Widespread</td>
<td>Widespread</td>
<td></td>
</tr>
<tr>
<td>IST-9</td>
<td>Widespread</td>
<td>Absent in adult tissues</td>
<td></td>
</tr>
</tbody>
</table>

Distribution of the isofrom (s) | Total FN | Isosforms containing the ED-A sequence | Isosform containing the ED-B sequence |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Widespread</td>
<td>Present in the vascular wall and the matrix of fetal tissues and tumours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

Furthermore, use of the cell proliferation marker MB-1 showed endothelial proliferation in arterioles, venules, and capillaries of the cerebral tissue neighbouring AVMs. The present findings indicate that a particular FN isoform, mainly expressed by the vasculature of fetal and tumorous tissues, as well as a TN isoform typically detected in the walls of vessels in anaplastic gliomas, also occur in AVMs and in vessels of adjacent cerebral tissue, but that both isoforms are absent in normal brain. This evidence provides further support to the hypothesis of ongoing angiogenesis in and around these lesions. The presence of angiogenic features in AVMs might result from maintenance of proliferating and remodelling potentials, or from a specific response to haemodynamic stress in vascular structures subjected to increased blood flow and pressure. Occurrence of these features also in vessels lying in areas peripheral to the nidus might be related to recruitment of the neighbouring vasculature, possibly dependent on focal ischaemia in the setting of arteriovenous shunting. However, the presence in apparently normal vasculature of molecules typically occurring in fetal tissues and malignancies indicates that cerebral AVMs may not be static lesions. Further studies are needed to ascertain whether this phenomenon results merely from haemodynamic stress or actually reflects an intrinsic growth potential. Should this second be the case, current therapeutic strategies would possibly require revision.

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

Hashimoto's encephalopathy presenting as "myxoedematous madness"

The neuropsychiatric sequelae of hypothyroidism range from lethargy and mental slowing to the florid psychotic illness referred to as "myxoedematous madness". The last condition is characterised by frank hypothyroidism accompanied by psychosis, and may respond completely to thyroxine. More recently described is a syndrome of subacute encephalopathy, associated with high titres of thyroid autoantibodies, raised CSF protein, EEG abnormalities, and perfusion deficits in the presence of normal structural neuroimaging. In most cases, the encephalopathy occurs without any gross change in circulating concentrations of thyroid hormones, suggesting that an inflammatory process is responsible for the cerebral dysfunction. In the absence of pathological data, the evidence for a specific pathogenetic mechanism is largely circumstantial: a small vessel vasculitis 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 thyroiditis. This suggestion would certainly be consistent with the range of clinical presentations of other autoimmune cerebral vasculitides. As autoimmune thyroiditis is the commonest cause of hypothyroid failure in this country, these conditions 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 aggressively threatened them with a saw. The general practitioner was called and suspected “alien hand syndrome”, a new psychoses, and a severe depressive illness. Police assistance was requested because of the patient’s continuing violent behaviour.

On admission he was unkempt but cooperative and not suspicious. He denied depression, but displayed no insight into the irregularity of his behaviour. No psychotic features were seen, although during the admission he consistently rationalised all reported psychiatric phenomena. He was aggressive towards staff and made repeated attempts to abscond. General physical examination was unremarkable. Neurological examination was normal except for spoken language which was fluent and grammatical, but contained word finding pauses, circumlocutions, and occasional semantic errors (for example, “I just want to get my feet back on the table”). Formal neuropsychological testing, and a screen of laboratory tests for reversible causes of encephalopathy, were performed on admission, and results are presented below (column A). Attention is drawn to his mild naming deficit, and poor performance on the Rey figure, which was due to planning rather than visuospatial errors, suggesting a predominantly “disexecutive” pattern. CT and EEG were both normal. Laboratory (units) A B

<table>
<thead>
<tr>
<th>laboratory test</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Urea and electrolytes</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>B12 and folate</td>
<td>Normal</td>
<td>Not tested</td>
</tr>
<tr>
<td>VDLR</td>
<td>Negative</td>
<td>Normal</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (mU/L)</td>
<td>58.4</td>
<td>0.87</td>
</tr>
<tr>
<td>Free T4 (pmol/L)</td>
<td>7.4</td>
<td>Not tested</td>
</tr>
<tr>
<td>Antithyroid microsomal antibody titres</td>
<td>1:25600</td>
<td>1:1600</td>
</tr>
<tr>
<td>Psychometric (normal/predicted range):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folstein MMSE (&gt;24)</td>
<td>25/30</td>
<td>25</td>
</tr>
<tr>
<td>NART IQ</td>
<td>10th percentile</td>
<td>16th percentile</td>
</tr>
<tr>
<td>WAIS-R (verbal)</td>
<td>13th percentile</td>
<td>Not tested</td>
</tr>
<tr>
<td>WAIS-R (performance)</td>
<td>27th percentile</td>
<td>Not tested</td>
</tr>
<tr>
<td>FAS verbal fluency (&gt;30)</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Cognitive estimate test (&lt;60)</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Digit span forwards (&gt;5)</td>
<td>10/30</td>
<td>16/30</td>
</tr>
<tr>
<td>Rey-Osterreith complex figure (copy) (36)</td>
<td>25.5</td>
<td>24</td>
</tr>
<tr>
<td>Rey-Osterreith complex figure (recall) (30%)</td>
<td>Not tested</td>
<td>75%</td>
</tr>
</tbody>
</table>

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, but there was no clinical evidence of thyroid failure other than the abnormal 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 thyroxine does not, in itself, imply that the cerebral illness had an endocrine origin; a recent report described a patient with a subacute encephalopathic illness and compensated hypothyroidism in the presence of increased antithyroid antibodies, all of which responded to thyroxine replacement alone.1 In that case, however, both EEG and SPECT were abnormal, the SPECT showing multiple areas of severely reduced perfusion, which normalised with treatment. By contrast, in the present case the EEG was normal and the SPECT abnormality was marginal and changed little if at all, with treatment. The evidence for a significant vasculitic component to the illness is therefore, unconvincing.

The mild and relatively circumscribed neuropsychological deficits coupled with florid psychotic phenomena, also contrast with the profound global disturbance of cognition usually associated with Hashimoto’s encephalopathy.3 This distinction suggests that microvascular disruption and thyroid hormone depletion may emphasise different aspects of the clinical range in Hashimoto’s encephalopathy. Although the present case would support Asher’s conclusion that the psychiatric features of Hashimoto’s encephalitis typically respond to thyroid replacement, it additionally suggests that subtle neuropsychological deficits may be apparent even in the absence of obvious cerebral perfusion deficits, and that these may not be fully reversible.

A CRAWFORD J R HODGES MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 2EF, UK

Alien hand sign in Creutzfeldt-Jakob disease

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

Creutzfeldt-Jakob disease, one of the human prion diseases, is characterised by rapidly progressive mental and motor deterioration.1 Involuntary movements occur in above 90% of the patients in the course of the disease, the most common being myoclonus.1 Other movement disorders range from tremor and festination to hemiballism and dystonia, and hemiballism.1 We report on a patient with CJD who presented with an alien hand.

Alien hand is a rare and striking phenomenon defined as “a patient’s failure to recognise the action of one of his hands as his own”.2 One of the patient’s hands acts as a stranger to the body and is uncooperative. Thus, there is loss of feeling of ownership but not loss of sensibility in the affected hand. Originally described in callosal tumours,3 the aetiology of alien hand also includes surgical callosotomy,4 infarction of the medial frontal cortex, opticocortical atrophy, and Creutzfeldt-Jakob disease,5 and corticobasal degeneration.6,7 A 70 year old, right handed Jewish man born in Argentina, living in Israel for the past 20 years, was admitted to the Neurology Department. Until a month prior to admission, he was apparently healthy and helped in the accounting office of the village where he lived. His neurological illness had presented insidiously during the past month with tiredness of gait and fine tremor.

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 con- vention, haemorrhagic, disrupted by hallucinations. The affect was sad and he had partial insight for his mental dysfunction. He was disoriented for time, place, and situation. He could understand speech and was able to follow instructions involving two consecutive components. Naming was preserved. Prominent dysphagia and dyscalculia were noticed. Immediate recall and short term memory were severely disturbed, whereas long term memory, especially for personal life events, was relatively spared. Abstract think- ing was severely affected. Bimanual move- ments, such as clapping, were extremely diffi- cult.

The cranial nerves were normal as were ocular fundus. The motor examination showed normal force. Deep reflexes were symmetric and plantar responses were flexor. The right arm had a dystonic posture. His gait was ataxic on a wide base.

At times, the left arm would spontaneously rise in front of the patient during speaking or while using his right hand. He was unaware of these movements until they were brought to his attention. When questioned about their purpose, the patient denied that they were voluntary. No grasping of either hand or foot was found. The patient had no cortical sensory loss.

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

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

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

The literature seems to describe distinct forms of alien hand. All share the occurrence of involuntary movements contrary to the patient’s stated intent, but the types of move- ment differ. In the callosal form, there are purposeful movements of the non-dominant hand. In the “mimetic” form, there is a grasping and utilisation behaviour of the dominant hand. In the corticobasal degeration, there are aimless movements of either hand.1 • When a consequence of a posterior 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 (espe- cially in patient 2). However, our case suggests that the alien hand sign in CJD may appear in a different type, performing less complex movements which resemble those reported by Riley et al in corticobasal degeration.2-5 These authors described the alien limb as “involuntarily rising and touch- ing the mouth and eyes” (patient 1). The patient thought that she “was powerless to stop this movement” and when directed to stop responded that “she didn’t”. Another patient’s left arm was at times “elevated in front of him”, while he was “unaware of this situation until his attention was called to it” (patient 10). Another related phenomenon coined as “arm levitation” was reported in progressive superanuclear palsy. In these patients the arm involuntarily raised and performed semi-purposeful movements.

One common denominator between CJD, corticobasal degeration, and progressive multifocal leukoencephalopathy, in which an alien hand sign has also been described, is multifocality. In corticobasal degeration, 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 sub- sequent isolation and disconnection.

We suggest that CJD should be added to the differential diagnosis of diseases present- ing with an alien hand with or without mo- clocus.

We are indebted to Professor Eran Zardeli, Depart- ment of Physiology, University of California, Los An- geles, USA. R INZELBERG P NISIPENAU S C BLUMEN R L CARASIO Department of Neurology, Hillel Yaffe Medical Center, Hadera, Israel

Correspondence to: Dr R Inzelberg, Department of Neurology, Hillel Yaffe Medical Center, Hadera, 38100, Israel. email neurology@hillel-yaffe.health.gov.il


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.1

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

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

At hospital admission, she was alert and mentally stable. Results of general physical examination were unremarkable. Neurologi- cal examination disclosed symmetric, pre- dominantly distal, weakness of the legs; 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/mm3.1 The results of the following investigations were within the normal limits: haemoglobin, erythrocyte sedi- mentation rate, serum urea, creatinine, electrolytes, creatine, glucose, transaminase, bilirubin, immunoglobulins (Igs), lead, iron, copper, urinalysis, urinary porphyrin, folic acid, and vitamins A, B1, B6, B12, and E. Anti- bodies to Campylobacter jejuni, Brucella melito- rius, Mycoplasma pneumoniae, and human T cell line reactivity were negative. Two pairs of acetylcholine receptor antibodies, specific and non-specific organ autoantibodies, IgA and IgG antiga- linid antibodies (AGA’s), IgA antiendomysial antibodies (EMAs), and IgA anticellular antibodies (ARA) assayed by enzyme linked immunoabsorbent assay (ELISA) and im- munofluorescence (IF) were also negative. Lumbar puncture was not performed. Anti- bodies against gangliosides GM1 and GT1b, myelin associated glycoprotein and myelin
basic protein were not tested. Nerve conduc-
tion studies were consistent with a predomi-
nately motor demyelinating peripheral neu-
ropathy (table). Her symptoms improved
spontaneously and she was discharged home
after 2 weeks. For 2 years she was asymp-
tomatic on a gluten free diet.

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

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

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

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

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

This patient, who was diagnosed as having
frank celiac disease at the age of 6 months,
shortly after she was introduced to the diet; and
the response to a gluten free diet was reasonably
rapid, occurring within weeks.

The present case, however, differs clinically
from those with neurological involvement pre-
viously reported. In the paediatric age group,
in fact, neurological complications of celiac
disease are rarely encountered and are mostly
confined to the CNS: to the best of our
knowledge, there are only two previously
reported cases of PNS involvement in children
with celiac disease. In both cases, however,
these were chronic axonal polyneuropathies
presenting during a gluten free diet.7 In both
episodes in the present case neuro-
physiology was strongly supportive of a
demyelinating peripheral neuropathy, which is
most commonly attributed to a direct immune
mediated attack to the myelin. By
contrast, wallerian and axonal degenerative
may be caused by vasculitis, and nutritional,
metabolic, and toxic factors.

An autoimmune pathogenesis in associ-
ation with strong evidence of a genetic
susceptibility has been proposed for celiac
disease. Although it is well established that
AGA, EMA, and ARA are reliable indicators
of sensitisation to gluten at least at the time of
diagnosis, in the clinical practice at follow up,
during a gluten challenge, pathological values
of these antibodies may not be detected.8 In
the present case the time course of the disease
might be suggestive of an antibody mediated
response. However, we could not detect
pathological concentrations of AGA, EMA,
or ARA antibodies either during the course of
the disease or at follow up.

It is known that in celiac disease many
immunological perturbations can occur out-
side the gastrointestinal tract. Crossing of
the antigens through a damaged small intestinal
mucosa, deposition of immune complexes in
target organs, a reduction in immune surveil-

lance, mechanism of molecular mimicry, and
activated T cell response may contribute to
the pathogenesis of the diseases associated
with celiac disease. Direct toxic effects of
gliadin and vitamin deficiency are other pos-
sible pathogenic mechanisms of damage to
the nervous system. Although we ruled out a
vitamin deficiency it is still questionable
whether a toxic neuropathy can be the case.

In conclusion this case shows two major
issues: an acute polyneuropathy can be a
complication of celiac disease in childhood
and its benign course could help in the
understanding of the underlying pathogenic
mechanisms. We are grateful to Professor Angela Vincent
(Oxford) for her helpful suggestions in reviewing the
manuscript.

AGATA POLIZZI
MARIA FINOCCHIARO
ENZO PARANO
PIERO PAVONE
Division of Paediatric Neurology, Department of
Paediatrics, University of Catania
Catania, Italy

Correspondence to: Dr Agata Polizzi, Division of
Paediatric Neurology, Department of Paediatrics,
University of Catania, Viale A Doria 6, 95125
Catania, Italy email: rupo@ctonline.it

1. Cooke WT, Thomas Smith W. Neurological
disorders associated with adult coeliac disease.
Brain 1966;89:683–722
disease, epilepsy and cerebral calcifications.
Nervous system involvement in childhood
celiac patients. In: Meanin ML, Mulder CJ, eds.
Coeliac disease. London: Kluwer Academic,
disease associated with peripheral neu-
ropathy in a child: a case report. Neuropediatrics
1998;29:155–9
antibodies in the various stages of coeliac
disease in children. Pediatr Med Chir 1988;10:
409–13

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.9 These soft signs include
primitive reflexes (frontal release sign),
resembling an anatomical and functional deaf-
ferentation of cortical from subcortical struc-
tures. Primitive reflexes are known to occur in a
wide variety of conditions, including
Alzheimer’s disease10 and vascular dementia.11
It is likely that the presence of undetected
cerebrovascular disease accompanying pe-
ripheral vascular disease is underestimated,
as peripheral vascular disease is known to be
a risk factor for transient ischaemic attacks. A
study assessing 373 older patients with
peripheral vascular disease found that 72 of
the 144 patients who had not experienced a
transient ischaemic attack, or stroke, were
found to have a degree of carotid stenosis of
between 60% and 99%.12

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

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

A more detailed description of instruments
is provided elsewhere.13 All subjects were

<table>
<thead>
<tr>
<th>1st Episode</th>
<th>2nd Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCV (ms)</td>
<td>26 27 74 74</td>
</tr>
<tr>
<td>DL (ms)</td>
<td>7.3 8.0 7.5 8.4</td>
</tr>
<tr>
<td>F wave latency (ms)</td>
<td>70 70 72 72</td>
</tr>
<tr>
<td>CMAP (µV)</td>
<td>3</td>
</tr>
<tr>
<td>SGV (ms)</td>
<td>Sural s 38</td>
</tr>
<tr>
<td>AMP (µV)</td>
<td>16.2</td>
</tr>
<tr>
<td>MCV: motor conduction velocity; DL: distal latency; CMAP: compound motor action potential; SGV: sensory conduction velocity; AMP: amplitude; L: left; R: right.</td>
<td></td>
</tr>
</tbody>
</table>
examine using a rating scale for the examination of frontal release signs (FRSS), with nine operationally defined items, each on a seven point semiquantitative scale. The nine reflexes were paratonia and 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 scale, and the controlled word association test) and generalised cognitive impairment (CAMCOG). Depression was assessed using the Hamilton rating scale for depression, 15 item geriatric depression scale, and diagnostic criteria for DSM IV major depressive disorder. Family history of depression, suicide to die, and suicidal ideation within the past year were also recorded, as were blood pressure and a checklist for chronic physical illness.

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

Patients with peripheral vascular disease had a higher mean score on the frontal release signs scale than controls (5.8 (SD 4.6) 1.7 (SD 1.0)). Mann-Whitney U=144.500, Z=−3.33, two tailed p=0.001, as well as on glabellar and rooting reflexes (table). Only one variable (trailmaking B test time) entered into the equation; this accounted for 23% of the variance in FRSS score (B=4.6, 95% confidence interval (95% CI) (B) 1.3–8.0, p=0.01).

In peripheral vascular disease, there is limited information available concerning the involvement of the neurological sequelae of coexisting cerebrovascular disease. Phillips et al found greater impairment in psychomotor speed and abstract reasoning in patients with peripheral vascular disease than age/sex matched controls, with less significant differences between the groups in verbal fluency, concentration, abstract thought, perception, and constructional skills.1 Another study by the same group found poorer performance in patients with peripheral vascular disease than age/sex matched controls on visual memory, trailmaking B test, and visuospatial skills. Patients with peripheral vascular disease were also equally impaired in these areas compared with a matched group of stroke patients.5

Small numbers of patients, which may also have obscured other significant findings between the two groups, limit the present study. However, there is some evidence that clinically relevant cerebrovascular disease may accompany peripheral vascular disease and that 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 Vreeling and Mr Paul Baskerville for allowing me to interview patients under their care. The study was carried out as part of a University of London MD thesis.

RAHUL RAO
Department of Old Age Psychiatry, Maudsley Hospital, Institute of Psychiatry, London

Correspondence to: Dr Rahul Rao, Department of Old Age Psychiatry, Guy’s, King’s, and St Thomas Medical School, Job Ward, Thomas Guy House, Guy’s Hospital, St Thomas Street, London SE1 9RT, UK email raarao@galabnet.co.uk


Factitious clock drawing and constructional apraxia

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

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

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

On transfer to this hospital the patient was alert, oriented, and cooperative. Although up to date on current affairs and able to describe the investigations performed at the transferring hospital, he scored only 23/30 on a mini mental state examination, with absent three word recall, impaired registration, and poor copying of a two dimensional design. Further bedside neuropsychological testing showed other findings indicative of constructional apraxia and left hemineglect. Specifically, when asked to draw a clock with the time at 10 minutes to 2 o’clock, all the numbers, and the clockhands, were placed on the right hand side of the clock outline (figure A). Copying of three dimensional line drawings was also significantly impaired (figure B). When asked to bilateral thrombolastin time/platelet activity was normal, as were carotid Doppler studies with a left hemiplegia. Brain CT at that time was normal, as were carotid Doppler studies and an echocardiogram. During that admission to hospital, several generalised seizure-like episodes were seen, some with retained consciousness, and he had again been started on phenytoin therapy. A follow up computerised brain MRI was normal and it was concluded that the hemiplegia was non-organic in origin. He was described to have made a gradual, near complete, recovery from this first hemiplegic episode and was scheduled for an imminent return to work at the time of his relapse.

Cranial nerve examination suggested an incongruent and inconsistent left hemianop sia to confrontation testing but was otherwise normal, including bilaterally symmetric otopokinetic 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 unremarkable.

Brain CT and MRI, CSF examination, and routine EEG were normal. Routine haematological and metabolic analyses plus erythrocyte sedimentation rate, serum lactate, prothrombin time/partial thromboplastin time, fasting serum glucose, HbA1c, serum Ig survey, and thyroid stimulating hormone were all within normal limits. A hypercoagulability profile was negative. A lipid profile showed mild hyperlipidaemia with increased low
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.

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

appropriately. Neurological examination showed contralateral gaze preference, supranuclear vertical gaze palsy, difficulty converging, left sided flaccid hemiparesis, and dense, left sided hemianesthesia. Deep tendon reflexes were absent on the left and Babinski’s reflex was present on the left. In addition, visual extinction and neglect were present. At the time of onset of right sided weakness the patient insisted that he was “fine,” and an ambulance was called over his objections. After being extubated, the patient acknowledged that he had had a stroke, but, despite his hemiparesis, insisted that he was ready to go home and go back to work. His belief in his ability to walk led to near falls, and he was marked as not “right sided” on the nurses’ admission 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, though he had previously recalled being otherwise. By this time he had a moderate hemiplegia and recognized “a little weakness,” but continued to insist that he was well and able to return to work. By the 6th week after his stroke, the patient more consistently acknowledged that he was weak on the left side of his body. A request for disabled housing “so that I won’t be a burden to my family” seemed to indicate an appreciation of his increased handicap, but his mood was shifted within an hour of making such statements the patient might insist that after a week’s exercise he would be ready to return to work. His awareness of his hemiplegia fluctuated for 8 weeks after stroke before becoming fixed, but remained shallow after 12 weeks; he no longer planned to return to work and applied for social security disability insurance “because they say I’m disabled.”

The patient’s mood was remarkably cheerful and optimistic. A week after the stroke he was noted to pray extravagantly the hospital food, and the nurses found him “talkative.” When he arrived on our ward 11 days after the stroke, he was visible with the nurse and staff and boasted of having fathered 64 children. His girlfriend was surprised when she kissed her in front of the staff because he had never previously shown affection before. He reported excellent energy and expansively invited all of the staff to his home for thanksgiving. Sleep was not interrupted 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 remained blissfully unconcerned. He scored to acknowledge his left sided weakness, he giving. Sleep was not disrupted or reduced reported excellent energy and expansively publicly displayed a section before. He re-

When he arrived on our ward 11 days after the stroke, he first acknowledged that his left arm belonged to him, though he had previously recalled being otherwise. By this time he had a moderate hemiplegia and recognized “a little weakness,” but continued to insist that he was well and able to return to work. His belief in his ability to walk led to near falls, and he was marked as not “right sided” on the nurses’ admission 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, though he had previously recalled being otherwise. By this time he had a moderate hemiplegia and recognized “a little weakness,” but continued to insist that he was well and able to return to work. His belief in his ability to walk led to near falls, and he was marked as not “right sided” on the nurses’ admission 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, though he had previously recalled being otherwise. By this time he had a moderate hemiplegia and recognized “a little weakness,” but continued to insist that he was well and able to return to work. His belief in his ability to walk led to near falls, and he was marked as not “right sided” on the nurses’ admission 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, though he had previously recalled being otherwise. By this time he had a moderate hemiplegia and recognized “a little weakness,” but continued to insist that he was well and able to return to work. His belief in his ability to walk led to near falls, and he was marked as not “right sided” on the nurses’ admission 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, though he had previously recalled being otherwise. By this time he had a moderate hemiplegia and recognized “a little weakness,” but continued to insist that he was well and able to return to work. His belief in his ability to walk led to near falls, and he was marked as not “right sided” on the nurses’ admission 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.
less commonly (only 1 of 74 seizures recorded). A review in 1996 of the “ictal bradycardia syndrome” showed only 15 documented cases in the literature of either bradycardia or asystole associated with seizures. Most patients had temporal lobe seizures. The longest duration of asystole previously reported is in a 17 year old man with temporal lobe epilepsy who sustained a 22 second pause in cardiac output. More typically the asystolic periods in documented cases are in the region of 5–10 seconds. Shorter duration asystole may not compromise cerebral function sufficiently to cause loss of consciousness. Implantation of a cardiac pacemaker is advocated but does not ensure that lapses of consciousness are eliminated if these are directly related to the seizure rather than to the secondary asystole. We report on a patient with epileptic cardiac asystole of 25 seconds duration demonstrated by prolonged simultaneous EEG/ECG monitoring which responded well to pacemaker insertion. A previously well 34 year old right handed builder was referred with a 1 year history of fortnightly episodes of loss of consciousness. There was no associated warning, aura, chest pain, or palpitations and the patient was only aware of the episode once consciousness was lost.
restored and he found himself lying on the floor. On recovery there was no confusion, drowsiness, dysphasia, or diuresis. Often, however, he sustained soft tissue injuries to his face and scalp.

Witnesses reported that the patient would, without warning, suddenly collapse to the ground where he would remain unresponsive, inaccessible, and motionless for 90 to 120 seconds. On two occasions he appeared confused and disoriented immediately before a collapse. During the period of unconsciousness he would demonstrate no involuntary movements, orofacial automatisms, or cyanosis but he would become pale and “ashen” while staring straight ahead with a glazed look. On one occasion of the episode his four-fingered grip would return to normal and within 2 minutes he would have fully recovered. Unusually during one recorded 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 fleeting 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 temporal lobe epileptic seizures. The thorax showed poor respiratory movement, and the patient showed paradoxical movement of the abdomen in the supine position. Tendon reflexes were hypoactive in all limbs. The patient’s sensations of touch and pain were mildly impaired in the four extremities.

In conclusion the peripheral myelin protein-22 (PMP-22) gene

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 who experienced 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 worsening of the diaphragm and lower limbs. At the age of 57, he experienced difficulty in getting up stairs. However, he was almost independent in daily life. At the age of 60, he was admitted to a local hospital with a history of respiratory failure with a coma due to CO, narcosis (PCO₂, 117.6, PO₂, 64.0). Responding to mechanical ventilatory support, he completely recovered consciousness within a day. His respiratory condition in the daytime improved to that previously. However, he needed mechanical ventilation during sleep because of nocturnal hyperventilation.

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

In a neurological examination, the patient’s mental state and cranial nerves were normal. Evidence of muscular atrophy and weakness of the diaphragm was noticed. The muscular atrophy was prominent in the shoulder girdle, intercostal muscles, paravertebral muscles, and pelvic girdle, and moderate atrophy was present in all four limbs (figure). There was moderate weakness of the shoulder and pelvic girdle and mild weakness of the distal limbs. The thorax showed poor respiratory movement, and the patient showed paradoxical movement of the abdomen in the supine position. Tendon reflexes were hypoactive in all limbs. The patient’s sensations of touch and pain were mildly impaired in the four extremities.

Moreover, pulmonary function tests were normal. No monoclonal or polyclonal proteins were detected. IgG and IgM antibodies to gangliosides GM1 and GD1b were negative. Analysis of CSF showed 1 lymphocyte/mm³ and 25 mg/dl protein. Motor nerve conduction studies showed prolonged distal latencies in the right median (8.8 m/s (normal value in our laboratory <4.6)) and ulnar (6.2 m/s (normal<3.6)) nerves, and moderate decreased conduction velocities in the right median (normal >45), ulnar (45 m/s (normal>49)), tibial (35 m/s (normal>38)), and peroneal (29 m/s (normal>41)) nerves. There were moderate decreases in the amplitude of compound action potentials in all the nerves tested, and an amplitude reduction of 50% was detected across the cubital tunnel of the right ulnar nerve. Minimum F wave latencies were prolonged in all the nerves tested. The latency in the right phrenic nerve was slightly prolonged EEG and ECG recordings were acquired, ictal arrhythmias occurred in 52% of seizures, the commonest being irregular abrupt changes in heart rate, (both accelerations and decelerations) occurring towards the end of the period of EEG abnormality. Interictally, patients with epilepsy seem no more likely than age and sex matched healthy subjects to experience arrhythmias although in one study patients with epilepsy had a faster ventricular rate and a longer QT interval than control subjects. It has been hypothesised that there is lateralisation with respect to central autonomic cardiac control with an increase in heart rate seen after an increase in activation of amygdaloid and inactivation of the left hemisphere and a decrease in heart rate on right hemispheric inactivation. Experimental stimulation of the rostral posterior insular cortex in anaesthetised rats has been shown to induce tachycardia and more causal regional stimulation to cause bradycardia. Additionally, prolonged stimulation resulted in ventricular ectopics, heart block, QT prolongation, and death. In pseudotemporal 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 a routine EEG. Recording solely the EEG or the ECG 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.

delayed (8.7 ms (normal<8.0)). Sensory nerve conduction studies showed a reduced amplitude of sensory nerve action potentials and conduction slowing in all the nerves tested. Electromyography carried out in the supraspinatus, deltoid, biceps, flexor carpi ulnaris, brachioradialis, quadriceps femoris, biceps femoris, tibialis anterior, and gastrocnemius muscles showed polyphasic motor unit potentials of long duration, but denervation potentials were rare. A left sural nerve biopsy showed scattered tomaculous thickening of the myelin sheath and some abnormally thin axonal myelin sheaths. The density of myelinated fibres was reduced (5726/mm²).

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

We examined the patient’s elder sister (64 years old), elder brother (62 years old), and younger sister (58 years old), although they had no neurological complaints. All of them had experienced generalised hyporeflexia or areflexia but no weakness or sensory loss, and nerve conduction studies showed moderate conduction slowing with accentuation at the common entrapment sites, suggesting demyelinating neuropathy. Our patient recalled experiencing recurrent episodes of transit entrapment mononeuropathies, and the familial occurrence of asymptomatic entrapment neuropathy was detected by nerve conduction studies. The presence of tomacula, and genetic analysis confirmed a diagnosis of HNPP. However, the patient’s dominant clinical features—respiratory failure and proximal muscle weakness—were atypical for HNPP. Although respiratory muscle weakness has been reported in hereditary motor and sensory neuropathy (HMSN), there has been no report of respiratory insufficiency associated with HNPP to our knowledge.

The weakness of the truncal muscles, including the respiratory accessory muscle, is a possible cause of respiratory failure in our patient. On the other hand, he had experienced hypotension 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 unrecognised in many cases. Concurrent ipsilateral spinal accessory neuropathy and internal jugular venous thrombosis after CEA is expected to be rare, and this is underscored by the 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. He was admitted to the cardiology ward and he presented for neurological evaluation 4 months after CEA. At that time, he had some induration along the incision site and a palpable supraclavicular cord. There was moderate atrophy of the right sternocleidomastoide 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. Electrodiagnostic studies were consistent with partial right accessory nerve neuropathy with minor denervation of the right trapezius. Cervical ultrasonography and MRI demonstrated right internal jugular venous thrombosis. The patient was treated with a shoulder support, analgesics, and low dose aspirin. There was no significant clinical change 1 year after CEA. Repeat electrodiagnostic testing was consistent with chronic right spinal accessory neuropathy, and repeat ultrasonography showed persistent right internal jugular venous thrombosis. Although the onset of spinal accessory neuropathy may be slow, this patient developed neuropathy 4 months after CEA.

Spinal accessory neuropathy was first described as a complication of CEA in 1982. Since then, there have been several case reports and small series. A 1996 review of reports of cranial neuropathy after CEA disclosed only one patient with spinal accessory neuropathy in over 3000 cases. Although the authors did not include several other reports which, taken together, may 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 nerve 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. 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. The spinal accessory nerve courses along the internal jugular vein and near the internal carotid artery, typically well above the carotid bifurcation. This should raise the possibility that 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 unclear.

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

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 perivascular induration, fever and leukocytosis may occur.

Common pathogenetic mechanisms for spinal accessory neuropathy and internal jugular venous thrombosis may include intraoperative traction, haematoma, and postoperative inflammation and scarring. Although the onset of 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 mechanism of injury.

GEORGE WOODWARD
RAM VENKATESH
Department of Neurology, University of Kansas, and Neurology Section, VA Eastern Kansas Health Care System, VA, USA

Correspondence to: Dr George Woodward, Neurology Section (111), VA Medical Center, Leavenworth, Kansas 66048, USA. Telephone 001 913 682 2000 extension 2441; fax 001 913 758 4225.


Ishaeic 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. The patient was a 33 year old man who had a severe headache on awakening on the morning of 23 January 1999. He did not complain of any other symptoms. He was referred to our department on 26 January 1999. He had a Wernicke aphasia with a slightly right sided face and arm weakness and a right Babinski sign.

Ishaeic 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. The patient was a 33 year old man who had a severe headache on awakening on the morning of 23 January 1999. He did not complain of any other symptoms. He was referred to our department on 26 January 1999. He had a Wernicke aphasia with a slightly right sided face and arm weakness and a right Babinski sign.

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

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

Although a paradoxical embolism through a patent foramen ovale in this patient cannot be ruled out as he recently returned from a transatlantic air flight, there was no deep venous thrombosis and D-dimers were normal. However, ephedrine has an indirect sympathomimetic action and is responsible for arteriolar vasconstriction in addition to other catecholaminergic effects. Both ischaemic and haemorrhagic stroke associated with ephedrine use have been reported.1 Acute myocardial infarction and acute psychosis have also been reported after taking ephedrine and other sympathomimetic drugs.2 Ephedrine and its metabolites are natural products that are used in non-prescription medications for multiple uses, and MaHuang extract (corresponding to 20 mg ephedra alkaloids) is available as an energy supplement in non-prescription tablets in some countries.

Although no carcinogenic side effects have been reported with the use of creatine monohydrate, this compound, used in association with other drugs as energy supplement may have deleterious side effects. This may be particularly true when used at high doses in combination with sympathomimetic drugs as in our patient. Renal dysfunction has also been reported after oral creatine supplements. Our patient had a slight increase in creatinine concentration although...
it remained in the normal range. Whether the use of high doses of caffeine can enhance the cardiovascular effect of ephedrine remains a possibility as stroke after taking a combination of caffeine and amphetamine has been reported.1

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

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

K VAHEDI
V DOMIGO
P AMARENCO
M-G BOUSSER
Service de Neurologie, Hôpital Lariboisière, Paris, France

Correspondence to: Dr K Vahedi, Service de Neurologie, Hôpital Lariboisière, 2 Rue A Paré, 75010 Paris, France
email vahedi@ccr.jussieu.fr


Petroclival meningioma as a cause of ipsilateral cervicofacial dyskinesias

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

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

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

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

The postoperative improvement of the dystonic and choreic grimacing and the cervical dystonia indicates a causal association between the petroclival meningioma and the segmental hyperkinetic movement disorders. Such a relation is supported also by the absence of a family history of movement disorders and the absence of previous exposure to nootropics. 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 paroxysmal dystonic neuromas, meningiomas, and epidermoid tumours of the cerebel-lopontine angle.2 Acoustic neuromas and anaplastic pontocerebellar glioma can be associated with facial myokymia and spastic paretic facial contracture.3 Also, cervical dystonia due to tumours of the cerebellopontine angle have been reported recently.4

The pathophysiological mechanisms responsible for dystonic movement disorders 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.5

Our case provides further evidence that functional impairment by compression and distortion of the brain stem may cause hyperkinetic cerebrofacial movement disorders. It is also supported also to know 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.

THOMAS POHLE
JOACHIM K KRAUSS
Department of Neurosurgery, Inselspital, University of Bern, Bern, Switzerland

JEAN-MARC BURGENDY
Department of Neurology

Correspondence to: Dr J K Krauss, Department of Neurosurgery, University Hospital, Klinikum Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany.
email joachim.krauss@nch.ma.uni-heidelberg.de


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.5 The mechanisms of action of trans-fer factor are still far from clear; in vitro dia-lysaile leucocyte extract increases macrophage activation and interleukin (IL) 1 production and enhances leucocyte chemo-taxis and natural killer function. Transfer factor has been reported to stimulate the cell mediated antigen specific response in patients with various infections;6 therefore, treatment with transfer factor has been suggested in patients with selective deficits in cell medi-ated immunity or for some refractory neoplasms and chronic infections. Moreover, it has been used in the treatment of uveitis.7 Administration of dialysable leucocyte ex tract has seemed to be free of hypersensitivity, long lasting side effects, or complications, except for transient hyperpyrexia.8

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 confu-sion, and right hemiparesis. He had had recurrent bilateral uveitis from the age of 12 to 14 with resolution of symptoms. In January 1995 retinal vasculitis was diagnosed at fundoscopy and in July 1995 he started oral transfer factor as dialysable leucocyte extract twice a week. He complained of gen-erally weakened after the second dose and the referring symptoms developed after the third dose.

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

Laboratory examinations on admission showed a slight increase in total serum protein (8.4 g/l, normal 6.0–8.0 g/l), although the serum protein fraction was normal, antistreptolysin tites (355 UI/ml, normal <200 UI/ml), and anticardiolipin IgG (30 UI/ml, normal <30 UI/ml). Negative results were obtained for blood and serum immunoglobulins, venereal disease research laboratory test, erythrocyte sedimentation rate, fibrinogenemia, C reactive protein, rheumatoid factor, Waaler-Rose, protein electrophoresis, antinuclear, anti-DNA, anti-smooth muscle, and antineutrophil cytoplasmic anti-bodies, lupus anticoagulants, cryoglobulins, immune complexes, complement fractions, and neoplastic markers.

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

Cell, protein, and glucose concentrations in CSF were normal. No oligoclonal bands or antibody against CMV, Hepes simplex, Varicella zoster, Epstein-Barr virus, Cossaxie, Adenovirus, Enterovirus or Borrelia burgdorferi were present. We report a patient in whom multiple cerebral white matter lesions developed after taking dialysable leucocyte extract orally for uveitis.
the diagnosis of vasculitis or neuro-Bechet's disease although in the absence of biopsy. In fact, the clinical, laboratory, and MRI findings were not typical and a low titre of anticardiolipin antibodies is found in 2% of healthy subjects.1

The occurrence at different time of focal cerebral white matter lesions highly supports the diagnosis of multiple sclerosis, but some clinical and laboratory findings in the 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.2 In addition, CSF without oligoclonal banding argues against a diagnosis of multiple sclerosis, whereas it is commonly found in acute disseminated encephalitis.3 On the other hand the possibility that acute disseminated encephalitis may recur has been accepted4 and on the basis of the patient’s clinical picture and CSF, we favoured such a diagnosis.

The pathogenic mechanisms underlying the triggering, development, and duration of multiple sclerosis and acute disseminated encephalitis are still far from clear despite the progress made in unravelling them. Some findings suggest that acute disseminated encephalitis and multiple sclerosis lie at the two poles of an autoimmune range, in which autoantigen reactivity is only temporary and direct against a single antigen in acute disseminated encephalitis and multiple antigens in multiple sclerosis.

Although the hypothesis that dialysable leucocyte extract had triggered an autoimmune disorder in our patient cannot be proved, our finding is in line with the report of multiple cerebral lesions after therapy with IL-2 in patients with malignancies or HIV infections.3 On the other hand, the fact that acute disseminated encephalitis is often correlated with the administration of foreign proteins, such as during vaccinations or viral infections led us to postulate in this patient a cell mediated immunological mechanism. Therefore, an immunological cross reaction between viral antigens (or other foreign material contained in vaccines) and various parts of the nervous system resulting in acute disseminated encephalitis might have occurred. As already noted, dialysable leucocyte extract contains a multitude of immunostimulating or potentially activating substances so it is impossible to pinpoint which one could have been responsible for the demyelinating effect seen in our patient. This notwithstanding, our finding indicates that neurological surveillance is worthy in patients assuming dialysable leucocyte extract therapy.

FRANCESCO G FOSCHI
LORENZO MARSIGLI
MAURO BERNARDI
Semeiotica Medica, Dipartimento di Medicina Interna, Epatologia e Cardioangiologia, Università di Bologna, Policlinico Sant’Orsola, via G Massarenti 9, 40138 Bologna, Italy. Telephone 0039 51 308943; fax 0039 51 308966; email: fgfoschi@tin.it


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 disease1—whether idiopathic or associated with hypoparathyroidism—previously been associated with this handicap. We present the case of a 24 year old man with Asperger’s syndrome, primary hypoparathyroidism, and multifocal brain calcifications.

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

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

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

Brain CT showed dense calcium deposits in the basal ganglia, thalamus, cerebellar dentate nucleus, and orbitofrontal cortex, consistent with Fahr’s disease (figure). Serum calcium was 0.8 mM (normal 2.5–6.3 mM). Serum parathyroid hormone was below 0.6 pmol/l and 25(OH)D (normal 1.0–6.55 µM/l), and a nuclear scan with 99mTc was unremarkable. Magnetic resonance imaging showed a retro-odontoid extradural mass that was homogeneous and isointense on T1 weighted signal, and debrided without enhancement after intravenous gadolinium contrast, and was compressing the upper cervical spinal cord (figure). The laboratory tests were normal, confirming the absence of rheumatoid arthritis, metabolic disease, or gout. Surgical removal via a transoral approach with a minimal bony resection was direct and provided sufficient space to obtain spinal cord decompression. It was followed by a posterior C1–C2 fusion. Macroscopically, the lesion had no capsule and resembled a hypertrophic ligamentum flavum. Microscopically, it was non-inflammatory, hypocellular, and ligamentary pieces found within the mass appeared fibrous and almost disintegrated. The patient regained normal neurological function. Over a 3 year follow up period there was no recurrence.

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

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

The craniovertebral junction can be affected by several pseudotumorous masses extradurally located, such as rheumatoid panus, hypertrophic non-union of odontoid fracture, post-traumatic cicatrix, synovial cysts, tumorous calcium pyrophosphate dihydrate crystal deposition, tophaceous gout, calcification of the posterior longitudinal ligament, synovial disease-like pigmented villonodular synovitis, and synovial chondromatosis. Hyper trophy of the atlantoaxial ligaments as a consequence of degenerative disease was recently recognised as an individual entity. Only five previous cases have been published. We add another case to the short series available in the literature, emphasising that the cause of the spinal cord compression is amenable to surgical removal, symptomatic patients should be diagnosed and treated without delay. A 66 year old woman presented with a rapid development of progressive spastic tetraparesis and an unremarkable medical history. There was no osteosclerosis or instability on plain cervical radiography and C T. A bone scan with 99mTc was unremarkable. Magnetic resonance imaging showed a retro-odontoid extradural mass that was homogeneous and isointense on T1 weighted signal, demonstrating no enhancement after intravenous gadolinium contrast, and was compressing the upper cervical spinal cord (figure). The laboratory tests were normal, confirming the absence of rheumatoid arthritis, metabolic disease, or gout. Surgical removal via a transoral approach with a minimal bony resection was direct and provided sufficient space to obtain spinal cord decompression. It was followed by a posterior C1–C2 fusion. Macroscopically, the lesion had no capsule and resembled a hypertrophic ligamentum flavum. Microscopically, it was non-inflammatory, hypocellular, and ligamentary pieces found within the mass appeared fibrous and almost disintegrated. The patient regained normal neurological function. Over a 3 year follow up period there was no recurrence.
Selective hemihypaesthesia due to tentorial coup injury against dorsolateral midbrain: potential cause of sensory impairment after closed head injury

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

Brain CT on admission showed a discrete and linear high density at the left ambient cistern without other intracranial lesions. On the next day CT showed an obscure low density 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 craniocebrovascular injury. Responsible lesions for sensory impairment, detectable by neuroimaging studies, almost always accompany associated neurological deficits. To our knowledge, a selective injury at the spinothalamic or trigeminothalamic tracts due to closed head injury has not been highlighted in the neurological literature.

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

The mechanism of midbrain injury in our patient was speculated to be due to tentorial coup injury based on MR images. The location of contusion was at the lower dorsolateral midbrain, coinciding with the tentorial edge level. Initiation of injury was the surface of the midbrain; however, due to the proximity of the tentorial edge to the midbrain on the injured side, tentorial contact to the midbrain supposedly occurred more readily. Brain MRI findings support the anatomical features of this traumatic 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 pre-conditioned 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. Therefore, when we see a patient with post-traumatic sensory deficit, the possibility of this tentorial injury should be kept in mind even in minor head injury.


CORRESPONDENCE

Toluene induced postural tremor

We read with interest the article by Miyagi et al and comment on the medical treatment of toluene induced tremor. Microdialysis experiments in rats have shown that inhalation of toluene increases extracellular \(\gamma\)-aminobutyric acid (GABA) concentrations within the cerebellar cortex which probably explains why GABA agonists including benzodiazepines (for example, clonazepam) are not very effective in toluene induced tremor and ataxia. Rat experiments also showed a 50% reduction in brain catecholaminergic neurons.\(^1\) Degeneration of certain cerebellar pathways is probably responsible for the loss of this dopaminergic innervation.\(^2\) Dopamine agonists could therefore be of potential interest in the treatment of toluene induced tremor. This hypothesis was explored in a recently described case,\(^3\) which showed remarkable clinical and iconographic similarities with that described by Miyagi et al: (a) long history of chronic toluene inhalation, (b) marked postural tremor, (c) progressive worsening of the symptoms despite absence 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 proved successful in the treatment of postural tremor in patients with heredodegenerative disorders in which the dentatorubro-olivary system is affected. In addition, there is evidence that catecholaminergic pathways are also involved in this type of ataxias, supported by loss of specific clusters of these neurotransmitters in the CSF of patients with heredodegenerative ataxias.\(^4\) In our patient, amantadine hydrochloride (100 mg twice daily) abolished postural tremor and ataxia completely over a 3 month period. Subsequently, the treatment was discontinued, which resulted in relapse of the tremor and ataxia. He was rechallenged to amantadine, which resulted in relapse of the tremor over a month period.

Hydrochloride (100 mg twice daily) abolished

We think that there are two problems with this study that should make the physician cautious about adopting this treatment approach such as ventrointermedius thalamotomy.

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

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

We think that there are two problems with this study that should make the physician cautious about adopting this treatment approach such as ventrointermedius thalamotomy.

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

We read with interest the article by Sasaki et al concerning the atypical form of amyotrophic lateral sclerosis (ALS). The pattern of muscular atrophy in these patients differed from that of typical ALS in that severe muscle involvement was confined to the upper limbs, predominantly the proximal portion and shoulder girdle, sparing the face and the legs until late in the disease’s course or until the terminal stage.

Over the past few years, we have noticed a growing interest in the renaming of this clinical form of ALS, which has its origins and predomination in the proximal muscles and upper limbs and little or no effect of either a bulbar nature or in the lower limbs.

Thus Hu et al coined the term flail arm syndrome, to describe a subgroup of patients affected by ALS that predominantly showed signs of lower motor neuron disease in the upper limbs, without significant functional involvement of other regions on clinical presentation. This subgroup of patients was clinically characterised by the display of progressive atrophy and weakness affecting the proximal muscles in the upper limb muscles in a more or less symmetric manner.

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

Other terms used in the past to refer to this form of ALS have been danging arm syndrome, suspended form, orangutan sign, dead arm sign, bifacial palsy, rizomelic amyatrophy, and the idea of naming it a distinctive phenotype of a neurogenic sequence of introducing from these 36 non selected patients a hypothetical single case that had a family history of tuberous sclerosis complex and a subependymal nodule which enhanced with gadolinium. The effect would be to remove the stated statistical significance (using Fisher’s exact test) and to alter the outcome and both of these explanatory variables.

Identifying the risk factors that can tell us which subependymal lesions will become invasive is important. As subependymal nodules and SEGAs seem to be histologically identical it is unlikely that pathologists will provide an answer. The study of Nabbout et al suggests some new hypotheses and reiterates some others. However, the definitive answer will not be provided by studies of selected samples but by follow up of a population based sample of patients with tuberous sclerosis complex. In the absence of such a study we would be cautious about implementing screening programmes based on what may be misleading criteria.
“man-in-the-barrel” syndrome has even been suggested.

Probably all these terms used to define this variation of ALS are synonyms for an older, well known condition, the scapulohumeral form, or the chronic anterior poliomyelitis reported by Vulpian in 1886 and known in Franca-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 scapulohumeral distribution (over 45 years of age) generally leads to ALS as a matter of course. 

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

1. The prevalence of this form of ALS constituted 10% of the ALS group as a whole (n=395). (2) The age of onset of this form (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 deltoideo (glenohumeral muscle) 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 cortical spongiosis and ALS can cause difficulty in diagnosis. The problem lies in the fact that cerebral spongiosis is a common condition. It is found in 83.5% of men and 80.7% of women over the age of 65. The faster progressive deterioration of the symptoms, the appearance of bulbar signs, and the absence of sensory symptoms and signs would favour the diagnosis of ALS.


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

Over many years, several researchers have recognised this peculiar distribution of muscle atrophy in clinical practice. The clinical manifestations consist of the muscular atrophy confined to the bulbar region and the arms (proximally dominant), absence of deep tendon reflex in the arms, almost normal deep tendon reflex in the legs, and subluxation of the shoulder joints. Some patients progress to bulbar involvement, and many terms have been coined to describe this peculiar pattern of the muscular atrophy such as dangling arm, orang utan sign, dead arm syndrome, amytrophic brachial diplegia syndrome, bulbar palsy and man-in-the-barrel syndrome. Some researchers classified into a category of motor neuron disease (ALS or spinal progressive muscular atrophy). However, others could not exclude the possible cause of cervical diseases such as dissociated motor loss in the upper extremity. In fact, these patients had cervical abnormalities such as cervical spinal stenosis, herniation of the posterior longitudinal ligament, discospondylosis, MRI, or myelography. By contrast with clinical awareness of this peculiar pattern of muscular atrophy, no pathological confirmation had been made until we first reported necropsy cases in our articles. Now, these patients with their peculiar pattern of muscular atrophy are considered to be ALS or a subtype of ALS. In my private opinion, “dangling arm syndrome” or “dead arm sign” seems to be the most suitable term depicting this type of motor neuron disease.

I agree with Hu et al reporting four important statistical discoveries in this form of ALS: the prevalence percentage of 10% of the whole ALS group, the similar age onset to the rest of ALS, a predominance among men (the male/female ratio was 3:1 in our study), and a longer median survival. It is clinically important to give wider publicity to the existence of this atypical form of ALS to avoid unnecessary surgical intervention for cervical abnormalities.

Shoichi Sasaki
Department of Neurology, Neurological Institute, Tokyo Women’s Medical College, 8-1 Kasumiga-cho, Shinjuku-ku, Tokyo 162-8666, Japan

MOTOR NEUROPATHY WITH LONGER MEDIAN SURVIVAL

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 transcortical magnetic stimulation induced absent or delayed corticofugal responses at the tongue, the authors ascribed isolated dysarthria to interruption of the corticobulbar path. On the whole, these results seem plausible, but we would like to comment on the underlying mechanism of isolated dysarthria.

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

To assess corticocerebellar tracts function, Urban et al investigated cerebral blood flow in patients with isolated dysarthria using HMPAO-SPECT. They concluded that the corticocerebellar tracts is preserved in isolated dysarthria because of no evidence for cerebellar diaschisis on SPECT. Their SPECT findings on cerebral 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. Language parapraxes are 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 co-incoordination of multiple organs necessary for speech formulation as well as language comprehension. Although interruption of the cortico-linguual pathways is a likely cause of isolated dysarthria, it should be borne in mind that damage to other descending and ascending projections may contribute to isolated dysarthria.

Josép Gamez
Carlos Cervera
González Codina
Servicio de Neurología, Hospital Gral, Universitari Vall d’Hebron, Passeig Vall d’Hebron 119-135, 08035 Barcelona, Spain.

Correspondence to: Correspondence to: Dr Josep Gamez, Servicio de Neurología, Hospital Gral, Universitari Vall d’Hebron, Passeig Vall d’Hebron 119-135, 08035 Barcelona, Spain. email: 12784gj@ccommb.es

Bungo Okuda
Hisa0 Tachibana
Division of Neurology, Fifth Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya

JOSEP GAMEZ
CARLOS CERVERA
AGUSTIN CODINA
Servicio de Neurología, Hospital Gral, Universitari Vall d’Hebron, Passeig Vall d’Hebron 119-135, 08035 Barcelona, Spain.


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 transcortical magnetic stimulation induced absent or delayed corticofugal responses at the tongue, the authors ascribed isolated dysarthria to interruption of the corticobulbar path. On the whole, these results seem plausible, but we would like to comment on the underlying mechanism of isolated dysarthria.

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

To assess corticocerebellar tracts function, Urban et al investigated cerebral blood flow in patients with isolated dysarthria using HMPAO-SPECT. They concluded that the corticocerebellar tracts is preserved in isolated dysarthria because of no evidence for cerebellar diaschisis on SPECT. Their SPECT findings on cerebral 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. Language parapraxes are 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 co-incoordination of multiple organs necessary for speech formulation as well as language comprehension. Although interruption of the cortico-linguual pathways is a likely cause of isolated dysarthria, it should be borne in mind that damage to other descending and ascending projections may contribute to isolated dysarthria.
Motor cortical excitability in Huntington's disease

We read with great interest the paper of Hanajima et al reporting that intracortical inhibition of the motor cortex is normal in patients with chorea of various origins. At variance with their results we previously found a reduced intracortical inhibition in a group of patients with genetically confirmed Huntington's disease. Hanajima et al suggest that the discrepancies between the two studies may reflect differences in patient selection as they included patients with early stage Huntington’s disease to “study the pathophysiology of chorea unaffected by other disorders movement.” They postulated that our cases, because of the reported correlation with a dyskinetic rating scale, had an advanced stage of the disease possibly with coexisting dystonia or rigidity. These assertions deserve some comments.

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

The discrepancies between the two studies are more likely to be explained, at least in part, by some methodological differences. For instance, the amplitude of the control response was larger in our set (approximately 1.0 mV compared with 0.3 mV in the study of Hanajima et al). This may induce a different sensitivity of the test, and the amount of intracortical inhibition in our normal controls is greater (see also) than in the study of Hanajima et al.

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


The authors reply:

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

The discrepancy between the two studies\[2\] may not be mainly due to the different stage of the disease between the two groups of patients. Although the duration of the disease is one factor to judge the disease stage, the severity of the disease (stage of the disease) is also positively correlated with CAG repeat number.

We may have to take CAG repeat number into consideration in comparisons. Unfortunately, however, we have no way to do such comparisons between these two studies. We could say, at least, that the 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 an intensity of the conditioning stimulus before we confirmed inhibition in studies of patients.\[1\] 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 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
intracortical inhibition is often decreased even in normal subjects. The 80% of the threshold for relaxed muscles must correspond to different values relative to the threshold for active muscles in patients from that in normal subjects. (2) The intracortical inhibition is disturbed by FV and FVd. This slight abnormality could be detected with their method but not with ours because their method has better sensitivity in detecting an abnormality than ours. Whichever is true, the intracortical inhibition must be normal or slightly disturbed in Huntington’s disease.

R HANAJIMA
Y UGAWA
Department of Neurology, Division of Neuroscience, University of Medicine, Ueno, Tokyo, 7-3-1 3-Hongo, Bunkyo-ku, Tokyo 113-8655, Japan


Hanajima R, Ugawa T, Terao Y, et al. Intracortical inhibition must be normal or slightly disturbed in Huntington’s disease. This slight abnormality could be detected with their method but not with ours because their method has better sensitivity in detecting an abnormality than ours. Whichever is true, the intracortical inhibition must be normal or slightly disturbed in Huntington’s disease.

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

Firstly, the physiological meaning of both formulae of CCP presented (CCP1 and CCP2, respectively) is questionable. The implication of both presented equations is that the instantaneous value of cerebral blood flow velocity (FV(t)) at a given moment t is equal to 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 FV (FVs, FVd) should be equal to (ABPs−CCP)/CVR and (ABPd−CCP)/CVR, respectively. However, it can be shown that the vascular resistance valid for the static pressure/flow connection (CVR0), concerning mean pressures and flows) is different from and in general much higher than resistances determining dynamic pressure/flow relations (CVR1) as in the case of pulsatile 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−CCP)/CVR (2)

F1 = A1/CVR1 (3)

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 + CVR1/CVR0 × CCP (5)

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

CCP2 = 0.5 × ABP + 0.5 × CCP

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

The second criticism concerns the correlation of the calculated CCP2 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 vasoconstriction. However, the relative contribution of both effects is critical for the limit of CCP.

Finally, I would be interested in the authors’ explanation of negative diastolic flow values as seen in Doppler spectra of arteries with a high vascular resistance (peripheral arteries, middle cerebral artery during strong hypocapnea). In the case of ABP>CCP and a small vessel collapse according to the model of the authors, CVR should increase towards = and FVd towards zero (equation 1). Negative flow values could, consequently, not occur.

I suggest that the relation between pulsatile pressure and flow should be better described using the concept of different static and dynamic resistances (CVR0 and CVR1). The driving pressure of the mean FV is more accurately given by cerebral perfusion pressure (CPP=ABP−ICP) than by ABP−CPP. Therefore, equation 2 changes to FV = (ABP−ICP)/CVR (6)

and equation 5 to CCP2 = ABP−(1−CVR1/CVR0) × CVR1/CVR0 × CCP (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”.

Rolf R Diehl
Department of Neurology, Krupp Hospital, Alfred-Krupp-Straße 45117 Essen, Germany


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

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

MAREK CZOSNYKA
PIOTR SMIELEWSKI
STEFAN PIECHNICK
Academic Neurological Unit, Box 167, Addenbrooke’s
Cambridge Clinical CRD 2QQ, UK
Correspondence to: Dr Marek Czosnyka
email MC141@MEDSCHL.CAM.AC.UK

1 Czosnyka M, Smielewski P, Piechnik S, et al. Critical closing pressure in cerebrovascular cir-
2 Burton AC. On the physical equilibrium of the small blood vessels. Am J Physiol 1951;141:
119–29.
4 Michel E, Hillairet S, von Twickel J, et al. Frequency dependence of cerebrovascular im-

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 exi-
tation of the globus pallidum internum is asso-
ciated with chorea-ballism in monkeys.1 Levodopa induced dyskinesias are currently thought to share a similar pathophysiology but recent findings also suggest that abnormal pacemakers in the sub-
thalamic nucleus (GPI) are in keeping with such a general principle, but the threshold to induce dyskinesias in the parkinsonian state is higher than in intact animals. The case recently described by Figueiras-Mendez et al.4 is extremely interesting as it suggests that func-
tional inhibition of the subthalamic nucleus by high frequency stimulation blocks levodopa induced dyskinesias. This is clearly at odds with the current pathophysiological model of the basal ganglia. Thus, the finding of Figueiras-Mendez et al4 rises the intriguing possibility that dyskinesias depend or are mediated by neuronal firing in a given region of the subthalamic nucleus, which was blocked by high frequency stimulation. Measurement of afferent synaptic activity by the technique of 2-deoxyglucose (2-DG) uptake showed an increment in the subtha-
lamical coefficients describing properties of the globus pallidum exter-
um), particularly in the ventromedial tip of the nucleus. This contrasts with the findings in monkeys with chorea induced by pharma-
cological blockade of the globus pallidum exter-
um, in which 2-DG uptake was maxi-
mal in the dorsolateral portion of the subtha-
lamical nucleus, where the sensorimotor region lies. A recent anatomical study5 also showed that the cortical-subthalamic nucleus con-
nexion is somatotopically segregated, so that fibres from the supplementary motor area project to the most medial portion and fibres from the primary and premotor areas termi-
nate in the lateral region of the subthalamic nucleus. All this heterogeneity may have pathophysiological relevance, one aspect of which could be the findings in the patient reported by Figueiras-Mendez et al.4 However, before the findings of this case may be used to sustain such a hypothesis on the role of the subthalamic nucleus in the origin of levodopa induced dyskinesias, there is a crucial issue to resolve—namely, the location of the tip of the stimulation electrodes.

There are several points leading us to question the actual site of action of the electro-
(1) Stimulation of the subthalamic nucleus in Parkinson’s disease has been asso-
ciated with the production of dyskinesias only on levodopa intake. Moreover, Benabid et al who pioneered this technique, consider the induction of dyskinesias by high frequency stimulation of the sub-
thalamic nucleus as a good indicator of a very positive response to the surgery. Dematting to the thalamic from the globus pallidum internum are placed dorsocaudally to the subthalamic nucleus and could be blocked by high frequency stimulation. (2) When the record-
ing electrodes are positionally blocked, a change in the background noise level; (3) a change in the background noise when entering the subtha-
lamical nucleus in sagittal planes 11 mm or less, neuronal activity is characterised by action potentials of large amplitudes (0.5–1 nV) with low background activity, tonically firing neurons, and absent sensori-
motor responses (“driving”). All these char-
acteristics seemed to be present in the patient discussed here. Neuronal activity in the sensorimotor region of the subthalamic nucleus is different from the above but on occasions the distinction may not be easy. Accordingly, it is very important to docu-
ment in more detail the findings in the case of Figueiras-Mendez et al.4 Ideally we would like to see the trajectory and length of the differ-
ent recording tracks, the effects of micros-
timulation, and the post-surgery MRI with measurements 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.

J A OBESO
G L INAZASORO
J GURIDI
E RAMOS
Hospital de Navarra, Pamplona, Spain
Correspondence to: J A Obeso, 30 Cizur Artea, Cizur Mayor, 31180 Navarra, Spain

2 Grossman AR. A hypothesis on the pathophysi-
ological mechanisms of depression of the levodopa or dopamine agonist-induced dyskinesia in Par-
4 Bergman H, Wichmann T, DeLong MR. Subthalamic nucleus stimulation improves directly levodopa-induced dyskinesias in Par-

Figueiras-Mendez et al reply

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

Recognition of the electrical activity of the subthalamic nucleus by basal ganglia cells is determined by the following criteria: (a) high frequency discharge (25 Hz or higher) within the nucleus1; (b) a tonic (regular), phasic (irregular) or a rhythmic pat-
tern of discharge; (c) response to voluntary/ passive movements. 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 the correlation with the EMG and the accelerometer re-
corded simultaneously. Artificial manual stop-
ping 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; (c) the activity of the cells within the subthalamic nucleus and zona incerta with proper characteristics; (d) a change in the background basal noise when entering the subthalamic nucleus. A higher activity is observed when the background noise is lower; (e) 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.1 All these points were fulfilled by the patient reported.

Considering the questions in the letter by Obeso et al, we make the following comments: (a) Action potential characteristics of basal ganglia units are easily recognised from the rest of the recording cells, and are not very common. The recordings shown in the article have amplitudes less than 0.3 mV and could not be considered large amplitude potentials. We start to record activity from 3 mm before entering the subthalamic nucleus, traverse the length of the subthalamic nucleus, and go further down several mm to encounter substantia nigra pars reticulata cells. Changes in the background activity are clearly recognised and are higher when entering the subthalamic nucleus. Enough cells are re-
corded along the tracks experimented with to recognise a large amplitude potential. The

J Neurol Neurosurg Psychiatry 2000;68:100–126
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 literature is the neuroprotective effect of 3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors or “statins” in cerebral ischaemia. Preliminary studies have shown that statins modulate brain nitric oxide synthase activity and NO production in a neuroprotective manner. Data from a murine model of ischaemic stroke demonstrate that prophylactic statin therapy reduces infarct size by about 30%, and improves neurological outcome in normocholesterolaemic animals.2 In this investigation, statin therapy directly upregulated endothelial NO synthase in the brain without altering expression of neuronal NO synthase. Recent findings also suggest that statin therapy influences the activity of dendrites of inducible NO synthase. Lovastatin has been shown to inhibit cytokine mediated upregulation of inducible NO synthase and production of NO in rat astrocytes and macrophages, and this inhibition may represent a potential mechanism of suppressing inflammatory responses that accompany ischaemia. Most interestingly, these preliminary findings suggest that statin therapy may modify the friendly and unfriendly faces of brain NO in a synergistically neuroprotective manner. These and other vascular effects of statins in cerebral ischaemia are potentially of great importance in human neuroprotection and ongoing studies such as the The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study3 will help clarify their role in human cerebrovascular disease.

CARL J VAUGHAN
Division of Cardiology, Department of Medicine, Weill Medical College of Cornell University, The New York Presbyterian Hospital, Starr 4, 525 E 68th Street, New York, New York 10021, USA

NORMAN DELANTY
Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence to: Dr Carl J Vaughan email evaughan@nyh.med.cornell.edu

BOOK REVIEWS


That neuroimmunology has come of age is demonstrated by the profusion of volumes published on the subject in recent years. This volume focuses on the central nervous system, and aims to satisfy the curiosity of both the effusive 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 central nervous system. There follows a chapter that integrates the neurobiology of multiple sclerosis with contemporary issues of aetiology, cell injury, and repair. Next, a chapter on inflammatory demyelinating diseases and syndromes of isolated demyelination, acute disseminated encephalomyelitis and allied conditions, and some of the syndromes of demyelination that are now accepted as part of the range of multiple sclerosis. The chapters on demyelinating disease are drawn to a close by a discussion of existing and experimental therapies for multiple sclerosis. The book continues with chapters on para-neoplastic disorders of the CNS, stiff man syndrome, neurological complications of...
connective tissue disorders, organ specific autoimmunity, sarcoidosis, and cerebral vasculitis.

Each chapter is an appropriate length and well referenced; the wood is always clearly visible between the trees. This book is sufficiently readable and small to be recommended as holiday reading. Its only drawback is that in making erudition so readily available, one risks being outshined yet again by one’s registrar.

JON SUSSMAN


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

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

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

CLARE GALTON


Organ transplantation, once medical exotica, is now almost 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 Service, 1997). Basic surgical techniques were established at the beginning of the century in canine models. Transplantation of these experiments to humans awaited safe and effective immunosuppression. Until the 1960s, the only forms of immunosuppression were radiation (total body or total lymphoid) and non-selective chemical reagents (benzene and tolune). Then the antiproliferative drug 6-mercaptopurine (6-MP) was introduced, followed shortly by a derivative, azathioprine, with improved oral bioavailability. Combined with corticosteroids, these allowed the first human solid organ transplants to be performed: in 1963, the first lung transplant in Mississippi and liver transplant in Colorado. Then in 1967 Christian Barnard captured the world’s imagination with the first heart transplant. His technique has been modified slightly since, but the increasing success of organ transplantation rests mainly on improved immunosuppression with drugs that selectively suppress lymphocytes by inhibiting lymphokine generation (cyclosporin A, tacrolimus), renal transduction (sirolimus, leflunomide), or differentiation (15-deoxypergualin). As a result, over the last 10 years in the United Kingdom, the 1 year survival of grafts has improved from 80% to 90% (kidney), 55% to 75% (liver), and 70% to 90% (heart/lung).

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

ALASDAIR COLES


Volume nine of the Current Issues in Neurodegenerative Disease series examines the interplay between cerebrovascular disease and dementia, particularly Alzheimer’s disease. Two hundred pages of what are essentially 20 brief review articles comprise this text, sadly without any illustrations. Put together the introduction to each chapter there is a certain sense of deja vu, although on the positive side each contribution is extremely well referenced. The book is divided into five sections covering the historical concepts of vascular and Alzheimer’s dementias, the arguments for a pure vascular dementia, the role of Alzheimer’s disease in the genesis of dementia after stroke, the contentious white matter changes on neuroimaging to dementia, and finally a short section examining practical questions such as the management of stroke in patients with dementia.

Although containing the most that their own right, stroke and Alzheimer’s disease do seem to cross paths more often than would be expected by chance alone, and more often than can be explained by the presence of unexplained angiopathy and recurrent lobar haemorrhages. Perhaps common genetic factors are responsible and here the APoE alleles are discussed. The comprehensive section on deep white matter lesions seeks to explain the connection further—and convinces the reader that there is still a lot which is not well understood. It is in this section particularly that illustrations are greatly missed. Brief mention is made of other conditions which may produce white matter changes and dementia such as CADASIL, cerebral lupus, and the primary antiphospholipid syndrome.

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

PETER MARTIN


Evolutionary biologists would probably tell us that the enchantment of stories is due to survival having been dependent on the passing of oral culture from one generation to the next. Information put in narrative form not only delights, but is easily recalled. Stories also construct meaning, supporting 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 of and use of narrative in clinical practice as a construct that can both

Childhood Epilepsies and Brain Development is the fruit of a symposium held in 1997 to try and bridge the chasm between those working in the clinic or at the bedside and those in the laboratory. Both groups must collaborate and communicate to improve the management of children (and adults) with epilepsy. The book is essentially a collection of monographs of heterogeneous content and style and the result, perhaps not surprisingly, is that some of the component parts are better than the sum. The clinically oriented section will clearly be of particular interest to those who treat children and their families. The chapters on infantile spasms and Lennox-Gastaut syndrome are informative and provide some new but speculative insights into the pathogenesis of spasms. However, it was surprising that severe myoclonic epilepsy of infancy did not merit a specific chapter in view of the unique electroclinical evolution and natural history of this syndrome. The crucial issue of the cognitive and behavioural sequelae of early and frequent seizures on the immature brain, which is probably of most concern to both clinicians and families, is succinctly addressed in two chapters—although a clear and consistent cause and effect relation remains to be established. The chapters covering basic neurophysiology, pharmacology, and neuropsychology are erudite and fascinating but at times are barely comprehensible. Further work is needed, including answering the fundamental question—why does the first seizure occur?—before the clinician and basic scientist are able to talk the same language—for the benefit of the patient with epilepsy.

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

RICHARD E APPLETON


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

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

The second half of the book is more of a mixed bag, both in terms of the areas covered and the quality of the chapters. A few 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. I would recommend because some aspects of the practical management of violence are missing—for example, a documented risk-benefit analysis, good failsafe communication, or deciding when to detain. One of the last chapters is a very good account of the management of hyperactivity in childhood, with good practical advice on the use of methylphenidate.

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

SIMON FLEMINGER

The Maudsley prescriptive 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 complemented on producing a guide of manageable size and ready accessibility.

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

There are a few cavils. The section on treatment of anxiety is skimpy (one and a half pages) compared with say the treatment of affective illness (22 pages) or schizophrenia (18 pages). The brevity is only partly explained by the undeveloped state of that particular area of psychopharmacology. Sections on common indications to and indications for lumbar puncture and indications for EEG seem to have been displaced from some other primer for busy junior doctors. There is no index.

These quibbles apart, prescribing guidelines can be wholeheartedly recommended.