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 Antiepileptic drugs were withdrawn to facilitate seizure recording.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

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

Both patients showed postictal psychosis and had a regional increase in rCBF over the right temporal neocortex and the left basal ganglia compared with their interictal study (figure). Quantitative analysis for patient 1 showed changes of ASI during IP and PP over right MT was +75% (-6.6476 to -1.65289); over the right LT was +116.78% (1.07927 to 12.55764); and over the left BG was +206.8% (-2.07373 to 2.21574). Quantitative analysis for patient 2 showed changes of ASI during IP and PP over right MT was -3.8% (1.31427 to 12.64158); over right LT was +178.6% (10.4696 to 18.70027); 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 partial seizure. Partial seizures were used to precipitate abrupt withdrawal of antiepileptic drugs.2 The cluster occurs in patients with poor drug compliance or during video EEG telemetry studies when antiepileptic drugs are withdrawn purposely. The clinical course of postictal psychosis is usually benign and predictable.3 In our patients, the duration of psychotic disturbances lasted from 10 to 14 days, which is in keeping with the good prognosis. Antipsychotic drugs, such as haloperidol and fluphenazine are usually used for treatment.

The underlying mechanism of postictal psychosis is unknown. Postictal cerebral hypofusion has been postulated as an analogue to Todd’s paralysis after seizure,4 5 However, the presence of increased rCBF during postictal psychosis, may suggest an alternative explanation as ictal SPECT has demonstrated seizure foci.6 During postictal psychosis, may suggest an alternative explanation as ictal SPECT has demonstrated seizure foci.6 During postictal psychosis, may suggest an alternative explanation as ictal SPECT has demonstrated seizure foci.6 During postictal psychosis, may suggest an alternative explanation as ictal SPECT has demonstrated seizure foci.6 During postictal psychosis, cerebral hyperperfusion areas are responsible for the postictal psychosis. Further serial studies with cerebral SPECT or PET may enhance our understanding on the mechanism of postictal psychosis.


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

<table>
<thead>
<tr>
<th>Anti-FN mAbs4 1</th>
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<tbody>
<tr>
<td>IST-4</td>
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<tr>
<td>IST-9</td>
</tr>
<tr>
<td>BC-1</td>
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<tr>
<th>Anti-TN Ab fragments4</th>
</tr>
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<tbody>
<tr>
<td>TN-12</td>
</tr>
<tr>
<td>TN-11</td>
</tr>
</tbody>
</table>

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<tr>
<th>Recognised isoforms</th>
<th>Total FN</th>
<th>Isoforms containing the ED-A sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Widespread</td>
<td></td>
<td>Isolates containing the ED-B sequence</td>
</tr>
<tr>
<td></td>
<td>Widespread</td>
<td>Absent in adult tissues (with the exception of the regenerating endometrium)</td>
</tr>
<tr>
<td></td>
<td>Widespread</td>
<td>Present in the vascular wall and the matrix of fetal tissues and tumours</td>
</tr>
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</table>

Oncofetal 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.6 7

Previous research from our laboratory disclosed that peculiar isoforms of fibronectin (FN) and tenasin (TN) typically occur in the vascular wall and the matrix of fetal tissues and tumours, with the recognised TN isoform occurring almost exclusively in fetal tissues and in tumours, with the recognised TN isoform being typically associated with anaplastic gliomas (table).

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 isoform in the inner layers of the vascular components of the nidus, irrespective of their morphology.

Six out of the 10 examined specimens were found to contain portions of cerebral tissue surrounding the angiomatous nidus. In all these cases the wall of several vessels exhibited intense staining with the use of the TN-11 Ab fragment. Using the BC-1 mAb some of these vessels exhibited some staining (figure). In the control specimens (brain and cerebellum) both the FN isoform containing the ED-B sequence (ED-B+FN) and the type III repeat C TN isoform were absent, despite the widespread distribution of total FN and TN in the vascular walls.
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 presence of angiogenic factors in AVMs might result from maintenance of proliferative 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 indicate that cerebral AVMs may not be static lesions. Further studies are needed to ascertain whether this phenomenon occurs 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 Dessi, 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 modulated 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, the condition has been present in at least some of Asher’s original 14 cases. Although most had florid myxoedematous features at psychiatric presentation, this may simply reflect the difficulty in diagnosing subclinical thyroid disease before rapid laboratory assays became widely available. Many features of the present case, however, favoured an endocrine rather than an inflammatory mechanism, suggesting that the condition of “myxoedematous madness”, though rare, remains a valid diagnostic entity.

A 63 year old market stallholder without medical or psychiatric history was brought to a local psychiatric hospital by the police. His business had been in decline for several months, and his family had noticed uncharacteristic emotional lability. In the weeks preceding admission he had experienced delusions and hallucinations, and exhibited uncharacteristic behaviour. He had reported a vision of the crucifixion, and hearing the voice of his dead mother. He claimed that his business had been destroyed, and that his house was occupied by the devil, drove around aimlessly in his car, and appeared constantly fearful and withdrawn. On the day of admission he had made a bonfire in the garden and burned his wife’s clothes, family photographs, furniture, and business papers. When his wife and son tried to intervene he
became aggressive and threatened them with a saw. The general practitioner was called and suspected a new psychiatric disorder. He denied depression, but displayed no insight into the irregularity of his behaviour. No psychotic features were seen, although during the admission he consistently rationalised all reported psychotic phenomena. He was aggressive towards staff and made repeated attempts to abscond. General physical examination was unremarkable. Neurological examination was normal except for spoken language, which was fluent and grammatical, but contained word finding pauses, circumlocutions, and occasional semantic errors (for example, “I just want to get my feet back on the table”). Formal neuropsychological testing, and a screen of laboratory tests for reversible causes of encephalopathy, were performed on admission, and results are presented below (column A). Attention is drawn to his mild naming deficit, and poor performance on the Rey figure, which was due to planning rather than visuospatial function. Formal psychometric 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 function.

<table>
<thead>
<tr>
<th>Laboratory (units)</th>
<th>A</th>
<th>B</th>
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<tbody>
<tr>
<td>Full blood count</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Erythrocyte 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>Normal</td>
</tr>
<tr>
<td>VDR</td>
<td>Negative</td>
<td>Not tested</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>1.74</td>
<td>Not tested</td>
</tr>
<tr>
<td>Antithyroid microsomal antibody titre</td>
<td>25/30</td>
<td>25/30</td>
</tr>
<tr>
<td>Psychometric (normal/predicted range):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithyroid microsomal antibody titre</td>
<td>1:2500</td>
<td>1:1600</td>
</tr>
<tr>
<td>WAIS-R (verbal)</td>
<td>10th percentile</td>
<td>16th percentile</td>
</tr>
<tr>
<td>WAIS-R (performance)</td>
<td>13th percentile</td>
<td>Not tested</td>
</tr>
<tr>
<td>FAS verbal fluency (&gt;30)</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Graded naming test (&gt;15)</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>

At 6 month follow up the patient had stopped neuroleptic drugs, but continued taking thyroxine. He reported feeling “back to normal”, but had bought a new psychic, and was a severe depressive illness. Police assistance was requested because of the patient’s continuing violent behaviour.

On admission he was unkempt but cooperative and appeared healthy. He denied depression, but displayed no insight into the irregularity of his behaviour. No psychotic features were seen, although during the admission he consistently rationalised all reported psychotic phenomena. He was aggressive towards staff and made repeated attempts to abscond. General physical examination was unremarkable. Neurological examination was normal except for spoken language, which was fluent and grammatical, but contained word finding pauses, circumlocutions, and occasional semantic errors (for example, “I just want to get my feet back on the table”). Formal neuropsychological testing, and a screen of laboratory tests for reversible causes of encephalopathy, were performed on admission, and results are presented below (column A). Attention is drawn to his mild naming deficit, and poor performance on the Rey figure, which was due to planning rather than visuospatial function. Formal psychometric 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 function.
were normal, as were folic acid, vitamin B12.

The patient had no cortical sensation. When questioned about their movements, such as clapping, were extremely difficult. Bimanual movements, such as clapping, were extremely difficult. The cranial nerves were normal as were the extrapyramidal, and cerebellar dysfunctions, such as clapping, were extremely difficult. 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 his use of these movements, the patient denied that they were voluntary. No grasping of either hand or foot was found. The patient had no cortical sensory loss.

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

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

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

The literature seems to describe distinct forms of alien hand. All share the occurrence of involuntary movements contrary to the patient’s stated intent, but the types of movement differ. In the callosal form, there are purposeful movements of the non-dominant hand. In the fronto-temporal form, there is grasping and utilisation behaviour of the dominant hand. In the corticobasal degeneration, there are aimless movements of either hand. When a consequence of a parasynaptic or vascular pathology, alien hands can perform complex acts such as trying to tear clothes or undoing buttons. The description by MacGowan et al. has characteristics of the callosal form (especially in patient 2). However, our case suggests that the alien hand sign in CJD may appear in a different type, performing less complex movements which resemble those reported by Riley et al in corticobasal degeneration.

One common denominator between CJD, corticobasal degeneration, and progressive multifocal leukoencephalopathy, in which an alien hand sign has also been described, is multifocality. In corticobasal degeneration, it was proposed that more than one site is affected or that a “release” phenomenon occurs accounting for the aetiology of alien hand. In CJD, bilateral cortical damage to motor areas might be the origin of their subsequent isolation and disconnection.

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

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

R Inzelberg
P Nisipeanu
S Blumen
R L Carasio
Department of Neurology, Hillel Yaffe Medical Center, Hadera, Israel

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


Recurrent peripheral neuropathy in a girl with celiac disease

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

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

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

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

Laboratory investigations showed a white cell count of 9300/mm³. The results of the following investigations were within the normal limits: haemoglobin, erythrocyte sedimentation rate, serum uric acid, creatinine, glucose, transaminase, bilirubin, immunoglobulins (Igs), lead, iron, copper, urinalysis, urinary porphyrin, folic acid, and vitamins A, B₁₂, B₆, and E. Antibodies to Candida albicans, Coxiella burnetii, Chlamydia psittaci, Toxoplasma gondii, antibodies to retrovirus antibodies, specific and non-specific organ autoantibodies, IgA and IgG antigliadin antibodies (AGAs), IgA antireticulum antibodies (EMA), and IgA antireticulin antibodies (ARA), assessed by enzyme linked immunosorbent assay (ELISA) and immunofluorescence (IF) were also negative. Lumbar puncture was not performed. Antibodies against gangliosides GM₁ and GQ₁ β, myelin associated glycoprotein and myelin...
basic protein were not tested. Nerve conduc-
tion studies were consistent with a predomi-
nately motor demyelinating peripheral neu-
ropathy (table). Her symptoms improved spontane-
ously and she was discharged home after 2 weeks. For 2 years she was asympto-
tic 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 includ-
ing burning paraesthesiae. On neurologi-
cal examination the legs showed marked diminution in muscle power; absent deep tendon reflexes, and a reduction in pain and temperature; light touch, perception of posi-
tion, and vibration were preserved. Walking was impaired and the patient was bedridden. Otherwise the examination was normal.

A haemogram showed white cell counts of 9700/mm$^3$. 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, experienced two episodes of acute peripheral neuropathy, at the age of 10 and 12 years, respectively. Two major pieces of evidence strongly support the assumption of a gluten derived disease: (1) the episodes occurred on both occasions when gluten was accidentally reintroduced in the diet; and (2) the response to a gluten free diet was reasonably rapid, occurring within weeks.

The present case, however, differs clinically from those with neurological involvement prev-
iously reported. In the paediatric age group, in fact, neurological complications of celiac disease are rarely encountered and are mostly confined to the CNS: to the best of our knowledge, there are only two previously reported cases of PNS involvement in children with celiac disease. In both cases, however, these were chronic axonal polyneuropathies presenting during a gluten free diet. 1

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

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

It is known that in celiac disease many immunological perturbations can occur out-
side the gastrointestinal tract. Crossing of the antigens through a damaged small intestinal mucosa, deposition of immune complexes in target organs, a reduction in immune surveil-
ance, mechanism of molecular mimicry, and activated T cell response may contribute to the pathogenesis of the diseases associated with celiac disease. Direct toxic effects of gliadin and vitamin deficiency are other 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 ENCO PARANO PIERO PAYONE
Division of Paediatric Neurology, Department of Paediatrics, University of Catania Catania, Italy

Coeliac disease associated with peripheral neu-

Papadatou B, Di Capua M, Gambazarra M, et al. Nervous system involvement in coe-

Simonati A, Battistella PA, Guarino G, et al. Coeliac disease associated with peripheral neu-


Frontal release signs in older people with peripheral vascular disease

A growing body of research examining neurological aspects of clinically “silent” cer-
ebrovascular disease suggests that neurologi-
cal signs indicative of generalised organic brain damage may occur in the absence of completed stroke. 1 These soft signs include primitive reflexes (frontal release signs), representing an anatomical and functional dea-
ferration of cortical from subcortical struc-
tures. Primitive reflexes are known to occur in a wide variety of dementia, including Alzheimer’s disease 2 and vascular dementia. 3 It is likely that the presence of undetected cerebrovascular disease accompanying pe-
ripheral vascular disease is underestimated, as peripheral vascular disease is known to be a risk factor for transient ischaemic attacks. A study assessing 373 older patients with peripheral vascular disease found that 72 of the 144 patients who had not experienced a transient ischaemic attack, or signs, rep-
Wright signs were found to have a degree of carotid stenosis of 60% and 99%. 3

In the present study, the prevalence of primitive reflexes was compared in a group of pe-
ple 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 opera-
tion were compared with 25 postopera-
tive patients who had undergone elective hip or knee replacement and a period of inpatient rehabiliation. All participants were aged 65 and over at the time of interview. Patients with peripheral vascular disease all had clini-
cal and Doppler proved evidence of periph-
ereal 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. 1 All subjects were


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cal signs indicative of generalised organic brain damage may occur in the absence of completed stroke. 1 These soft signs include primitive reflexes (frontal release signs), representing an anatomical and functional dea-
ferration of cortical from subcortical struc-
tures. Primitive reflexes are known to occur in a wide variety of dementia, including Alzheimer’s disease 2 and vascular dementia. 3 It is likely that the presence of undetected cerebrovascular disease accompanying pe-
ripheral vascular disease is underestimated, as peripheral vascular disease is known to be a risk factor for transient ischaemic attacks. A study assessing 373 older patients with peripheral vascular disease found that 72 of the 144 patients who had not experienced a transient ischaemic attack, or signs, rep-
Wright signs were found to have a degree of carotid stenosis of 60% and 99%. 3

In the present study, the prevalence of primitive reflexes was compared in a group of pe-
persons 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 opera-
tion were compared with 25 postopera-
tive patients who had undergone elective hip or knee replacement and a period of inpatient rehabiliation. All participants were aged 65 and over at the time of interview. Patients with peripheral vascular disease all had clini-
cal and Doppler proved evidence of periph-
ereal 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. 1 All subjects were
examined using a rating scale for the examination of frontal release signs (FRSS), with nine operationally defined items, each on a seven point semi-quantitative scale. The nine reflexes were patellar and palmen-tal, hand grasp, foot grasp, glabellar, rooting, snout, and visual/tactile sucking reflexes. Neuropsychological measures included the assessment of frontal lobe function (trailmaking tests A and B, behavioural dyscontrol scale, and the controlled word association test) and generalised cognitive impairment (CAMCOG). Depression was assessed using the Hamilton rating scale for depression, 15 item geriatric depression scale, and diagnostic criteria for DSM IV major depressive disorder. Family history of depression, wish to die, and suicidal ideation within the past year were also recorded, as were blood pressure and a checklist for chronic physical illness.

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

<table>
<thead>
<tr>
<th>Primitive Reflex</th>
<th>Hand grasp</th>
<th>Foot grasp</th>
<th>Glabellar</th>
<th>Palmen-tal</th>
<th>Patania</th>
<th>Rooting</th>
<th>Snout</th>
<th>Sucking (tactile)</th>
<th>Sucking (visual)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>U</strong></td>
<td>274.0</td>
<td>312.5</td>
<td>199.5</td>
<td>287.5</td>
<td>287.0</td>
<td>235.5</td>
<td>287.5</td>
<td>261.0</td>
<td>287.5</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>0.15</td>
<td>1.0</td>
<td>0.001*</td>
<td>0.15</td>
<td>0.29</td>
<td>0.01*</td>
<td>0.44</td>
<td>0.08</td>
<td>0.30</td>
</tr>
</tbody>
</table>

*Higher mean score in people with peripheral vascular disease.

Small numbers of patients, which may also have obscured other significant findings, were compared 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 neurologic 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.

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

5 years earlier. The angioplasty was complicated by the occurrence of 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 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 shape. Further bedside neuropsychological testing showed other findings indicative of constructonal 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 clock hands, were placed on the right hand side of the clock outline (figure A). Copying of three dimensional line drawings was also significantly impaired (figure B). When asked to bisect a straight line, the patient did so only minimally to the right of the midpoint (58% of the distance from the left side).

Cranial nerve examination suggested an incongruent and inconsistent left hemianop-sia to confrontation testing but was otherwise normal, including bilaterally symmetric optokinetic nystagmus. Motor examination showed paralysia 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. Vibration on the left side of the forehead, with a distinct demarcation in the midline. Vibration on the left side of the forehead, with a distinct demarcation in the midline.

Facultitious clock drawing and constructional apraxia

A 45 year old man presented with a 1 day history of headache, possible seizures, and left sided weakness. On the day of presenta-tion the patient’s wife had twice found him, incoherently, on the floor. After the second such episode she brought him to hospital for evaluation. Examination disclosed a complete left hemiplegia and hemianaesthesia, 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 further possible angiography and further investiga-tions.

He was an ex-smoker with hypercholester-o-laemia and peripheral vascular disease which had been treated by a left femoral angioplasty and constructional skills.5

Table 1: Primitive reflexes in patients with peripheral vascular disease (n=25) and controls (n=25)
density lipoprotein (3.92 mmol/l) and triglycerides (4.30 mmol/l) and low high density lipoprotein (0.73 mmol/l). Serum phenytoin concentration was therapeutic at 74 µmol/l. An ECG was normal.

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

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

A formal neuropsychological assessment performed in hospital documented impaired attention, concentration, and working memory, as well as several atypical calculation and spelling errors, the second involving unusual “near miss” letter substitutions or unusual “near miss” letter substitutions or reversals (for example, “amnesty”, “execuitive”). The formal testing identified no consistent evidence of visuospatial deficits or constructional apraxia. The findings were interpreted as inconsistent with the patient’s history but the possibility of a factitious actiology was not specifically addressed—that is, tests designed to detect malingering during neuropsychological testing were not administered by the examiner, who had not been informed at the time of consultation of the presumptive neurological diagnosis of malingering or factitious disorder.

No further investigations were performed and the patient was transferred via the original hospital to a rehabilitation facility and subsequently discharged to home. Confronted with the findings of the video monitoring the patient appeared sanguine and accepting of the evidence that he should be able to move his left side. Six months later he was amputating but otherwise not significantly improved. He had been assessed by a psychiatrist but had refused psychiatric follow up, electing instead to be followed up by a psychologist. He understood his diagnosis to be “conversion disorder” and reported that he was actively collecting information on the subject via the internet.

Outpatient brain SPECT and visual and somatosensory evoked potentials performed 1 year after discharge demonstrated no hemispheric abnormalities. The patient remained off work and was receiving disability funding. He walked with a limp favouring his left side and complained of persistent decreased sensation on the left side. Forced choice sensory testing of finger and arm movement on the left demonstrated performance to be worse than chance (68% wrong choices). Motor bulk, tone, and reflexes were symmetric and plantar responses downgoing. He drew a clock normally at the 1 year follow up.

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

The inability to copy line drawings or to draw a clock is, from a neurologist’s perspective, typically associated with parietal lobe dysfunction, usually of the non-dominant hemisphere, especially if associated with left hemispatial neglect. To our knowledge, this is the first reported case of factitious clock drawing and constructional apraxia. Bedside mental status testing also demonstrated the more common simulated deficits of impaired attention and absent three word recall. In retrospect, the severe neglect on clock drawing was perhaps “too good to be true”, especially in the light of the near normal line bisection demonstrated on the same day. The mirror image distortion of the house was also very unusual and, furthermore, the mirror reversal itself is evidence of lack of clinical neglect. The distortion of the cube, however, could easily be misinterpreted as evidence of organic constructional impairment if seen in the absence of the other relevant clinical and laboratory information.

During follow up, the patient admitted to feeling tremendous occupation related stresses, and described how he had come to both fear and detest his job. Given the clear benefit to the patient of removal from his work environment, the relapse of his symptomatology just as he was scheduled for return to work after his first non-organic hemispheric episode, and the intentionality required to feign poor clock drawing and constructional apraxia, there is much to support a diagnosis of malingering. Nevertheless, classification as a factitious disorder is at least as justifiable in view of the patient’s willingness to undergo medical investigations, including video monitoring.

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

Anosognosia and mania associated with right thalamic haemorrhage

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

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

On admission he was described as “belligerent,” “agitated,” and “confused.” Blood pressure was 240/160. Neurological examination disclosed left lower facial droop, decreased left corneal and gag reflexes, and left hemiparesis with dense sensory deficits. With increasing obtundation, the patient was transferred to the intensive care unit and intubated. Brain MRI showed a large, left sided, hyperacute thalamic bleed with mass effect and oedema. The patient was extubated 2 days later and 4 days after the stroke he was described as being drowsy and inattentive, but was able to answer questions
appropriately. Neurological examination showed contralateral gaze preference, supra-nuclear vertical gaze palsy, difficulty converging, left sided flaccid hemiparesis, and dense, left sided hemianesthesia. Deep tendon reflexes were absent on the left and Babinski's response was planter. This was consistent with 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 extricitated, the patient acknowledged that he had had a stroke, but, despite his hemiparesis, insisted that he was ready to go home and go back to work. His belief in his ability to walk led to near falls, and he was more easily heard by the nurses versus their 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 was "smelled funny" was another reason he wanted the nurses to take it away.

Four weeks after the stroke he first acknowledged that his left arm belonged to him and had been "someday" and not otherwise. By this time he had a moderate hemiplegia and recognized "a little weakness," but continued to insist that he was well and able to return to work. By the 6th week and after patient more consistently acknowledged that he was weak on the left side of his body. A request for disabled housing so that he wouldn't be a burden to his family seemed to indicate an appreciation of his impaired insight and was being shared within an hour of making such statements the patient might insist that after a week's exercise he would be ready to return to work. His awareness of his hemiplegia fluctuated for 8 weeks after stroke before becoming fixed, but remained shallow after 12 weeks; he no longer planned to return to work and applied for social security disability insurance because they say I'm disabled.

The patient's mood was remarkably cheerful and optimistic. A week after the stroke he was noted to praise extravagantly the hospital because he had never been so well in his life. Other than alcoholism, the patient had no history of psychiatric illness and there was no family history of psychiatric illness. The patient had not seen a physician in many years. Visual acuity was found to be reduced to 20/70 right eye on the basis of hypertensive retinopathy.

Evaluation 1 month after stroke showed many deficits and a few strengths. Inattention to the left hemispace was marked. By 2 months after stroke he no longer distinguished double simultaneous stimulation, but, although he could see to the left, was still missing targets in his left visual hemifield. Visual integration, both with and without the requirement of construction, was severely impaired. He was able to correctly recognize and produce facial emotional information. Simple attention was intact, but attentional control (backward span and mental control) was impaired. Visuomotor tracking was slow and he had significant problems with conceptual shifting (at the motor, visual). Language processing difficulties included very poor reading ability, impaired confrontation naming, and impaired performance on a verbal task of fluency and initiation. Auditory comprehension was mildly impaired. Vocabulary scored formally in the borderline impaired range, as did abstract verbal reasoning. On tests of praxis he demonstrated a tendency to use the hand as object. Memory performance was intact. His initial recall of two paragraphs scored formally within the low average range and after a 30 minute delay, he was able to recall most of the information initially encoded, scoring formally within the average range.

Structural brain MRI on admission to the emergency room showed a large right thalamic hemorrhage with mass effect and oedema, with oedema extending into the cerebral peduncle and right thalamus. Susceptibility consistent with deoxyhaemoglobin. Also present was increased T2 signal bilaterally in frontal areas consistent with ischaemic changes. Brain CT 30 days after stroke showed, in a patient with severe unilateral hemiparesis, moderate cerebellar atrophy and mild to moderate prominence of the frontal cortical sulci compatible with cerebro atrophy. Structural MRI performed 44 days after the stroke showed a 2 cm area of absent thalamus. Functional MRI performed the same day demonstrated a 2 cm area of absent cerebral blood volume at the posterior margin of the right thalamus without any evidence of decreased cerebral blood volume within the right parietal, frontal, or temporal cortex.

This is a case of anosognosia of hemiplegia and mania co-occurring in a patient with a large right thalamic haemorrhage. Although anosognosia and mania are not generally thought of as occurring together, when Babinski's introduced the term anosognosia he described one of his examples as a case in which the patient, though not confused, was "a little overexcited," and in a later paper he presented a case in which there was "a certain agitation, which expresses itself by exaggerated loquacity, a decrease in attention, and a tendency to erotic ideas." Weinstein and Kahn noted that euphoria was common in patients with anosognosia. Moreover, although Cutting emphasized that apathy is the mood more usually associated with anosognosia, 10% of his patients with anosognosia were described as having "euphoric mood."

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

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

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

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

ELIZABETH LIBSON
Department of Psychiatry, Tufts New England Medical Center, 750 Washington Street, Box 1007, Boston, MA 02111, USA. Telephone 001 617 636 1633; email eliebson@opal.tufts.edu

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Epileptic cardiac asystole

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

Cardiac arrhythmias subsequent to epileptic seizures have been recognised for more than 90 years. They provoke diagnostic confusion and may be a mechanism of sudden unexplained death in epilepsy. Whereas sinus tachycardia was noted to accompany more than 90% of epileptic seizures, isolated bradycardia was seen much

Medical Center, 750 Washington Street, Box 1007, Boston, MA 02111, USA. Telephone 001 617 636 1633; email eliebson@opal.tufts.edu

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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 restored.

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

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

He was admitted to his local hospital and CT, MRI, interictal EEG, and 24 hour ECG were normal. No episodes were witnessed while he was an inpatient but they were thought to be atonic 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. Cardiac and neurological examination was normal as were MRI and routine interictal EEG. Sixteen channel ambulatory EEG using an Oxford Instruments digital EEG receiver was performed continuously for 340 hours before an episode was captured. Interictally rare spikes were seen over the right frontocentrotemporal region during sleep. The ictal EEG/ECG recordings were acquired, ictal arrhythmias occurred in 52% of seizures, the commonest being irregular abrupt changes in heart rate, (both acceleration and deceleration) occurring towards the end of the period of EEG abnormality. Interictally, patients with epilepsy seem no more likely than age and sex matched healthy subjects to experience arrhythmias although in one study patients with epilepsy had a faster ventricular rate and a longer QT interval than controls.9

It has been hypothesised that there is laterisation with respect to central autonomic cardiac control with an increase in heart rate seen after an increase in stimulation of amobarbital 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 caudal region stimulation to cause bradycardia.10 Additionally, prolonged stimulation resulted in ventricular ectopies, heart block, QT prolongation, and death. In presurgical temporal lobeectomy patients stimulation of the left insular cortex (particularly posteriorly) produced bradycardia and a depressor response significantly more often than tachycardia and a pressor effect. It was suggested that an epileptic discharge in the insular cortex may result in cardiac arrhythmias. Recurrent episodes of loss of consciousness are a common clinical problem. An accurate diagnosis relies principally on the patient’s and witnesses’ accounts of events. Further investigations are frequently required which are often normal unless an episode is captured during monitoring. Recording solely the EEG or the ECG may result in erroneous conclusions being drawn and insufficient or inappropriate therapy being instituted. Distinction between a primary cardiac arrhythmia and a secondary central arrhythmia is possible only with simultaneous EEG/ECG recordings.

FERGUS J RUGG-GUNN
JOHN S DUNCAN
SHEEHAN J M SMITH
Epilepsy Research Group, University Department of Clinical Neurology, Institute of Neurology, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK

Correspondence to: Professor John S Duncan, National Society for Epilepsy, Chalfont St Peter, Gerrards Cross, Bucks SL9 0RJ, UK email j.duncan@ion.ucl.ac.uk


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.1 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 exhibited respiratory failure and proximal muscle weakness were prominent features.

The patient started to have dyspnoea on exertion at the age of 44. At the age of 47, he noticed a slowly progressive weakness of the pelvic girdle and lower limbs. At the age of 57, he experienced difficulty in going up stairs. However, he was almost independent in daily life At the age of 60, he was admitted to St Mary Red Cross Hospital with a comatose patient with a coma due to CO, narco-

sis (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 any 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 a scoliosis lordosis was found. The muscular atrophy was prominent in the shoulder girdle, intercostal muscles, paravertebral muscles, and pelvic girdle, and moderate atrophy was present in all four limbs (figure). There was moderate weakness of the shoulder and pelvic girdle and mild weakness of the distal limbs. The thorax showed poor respiratory movement, and the patient showed paradoxical movement of the abdomen in the supine position. Tendon reflexes were hypotonic in all limbs. The patient’s sensations of touch and pain were mildly impaired in the four extremities. The patient's body weight was normal. His vital capacity was 1.9 l (55% of the normal mean) in the sitting position, but 1.3 l (38%) in the supine position. The percentage of forced expiratory volume in 1 second (FEV1) was normal (99% of predicted). The chest roentgenography at inspiration and expiration showed poor movement of the diaphragm but no abnormality in the lung field. Routine haematological and serological studies gave normal results. No monoclonal or polyclonal 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 ms (normal value in our laboratory <4.6)) and ulnar (6.2 ms (normal<3.6) ms) nerves, and moderate decreased conduction velocities in the right median (normal>45), ulnar (45 ms (normal<49), tibial (35 ms (normal>38)), and peroneal (29 ms (normal>41)) nerves. There were moderate decreases in the amplitude of compound action potentials in all the nerves tested, and an amplitude reduction of 50% was detected across the cubital tunnel of the right ulnar nerve. Minimum F wave latencies were prolonged in all the nerves tested. The latency in the right phrenic nerve was slightly

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Delayed (8.7 ms (normal<8.0)). Sensory nerve conduction studies showed a reduced amplitude of sensory nerve action potentials and conduction slowing in all the nerves tested. Electromyography carried out in the supraspinatus, deltoid, biceps, flexor carpi ulnaris, brachioradialis, quadriceps femoris, biceps femoris, tibialis anterior, and gastrocnemius muscles showed polyphasic motor unit potentials of long duration, but denervation potentials were rare. A left sural nerve biopsy showed scattered tomacular thickening of the myelin sheath and some abnormal thin axonal myelin sheaths. The density of myelinated fibres was reduced (5726/mm²). A gene analysis disclosed a 53% gene dose of PMP-22 related to normal controls, using Southern blots of DNA digested with EcoRI. Given the possibility of superimposing demyelinating neuropathy, especially chronic inflammatory demyelinating polyneuropathy, oral prednisolone (60 mg/day) was given for 1 month. However, the patient’s clinical condition did not respond to this treatment. Pulmonary dysfunction and proximal muscle weakness were almost steady during the next 3 years.

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

The weakness of the truncal muscles, including the respiratory accessory muscle, is a possible cause of respiratory failure in our patient. On the other hand, he had experienced hypventilation in the supine posture and paradoxical movement of the abdomen, which suggested diaphragmatic weakness. Also, chest radiography showed poor movement of the diaphragm. Although the prolongation of distal latency in the phrenic nerve was mild considering the severity of respiratory failure, assessment of axonal loss is not possible with phrenic nerve stimulation. In fact, phrenic nerve latency is not necessarily associated with pulmonary dysfunction in HMSN. Diffuse proximal weakness in our patient is an uncommon finding as for HNPP. Mancardi et al. reported on three patients with progressive sensory-motor polyneuropathy associated with 17p11.2 deletion, and the initial symptom of one patient was proximal weakness in one arm. We propose that our patient represents a clinical phenotypic variability among HNPP. It may be necessary to pay attention to respiratory function in HNPP.

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.\textsuperscript{3} Concurrent ipsilateral spinal accessory neuropathy and internal jugular venous thrombosis after CEA is expected to be rare, and this is underscored by the lack of published cases. Despite this apparent rarity, a common pathogenetic mechanism for postoperative spinal accessory neuropathy and internal jugular venous thrombosis may well be present, at least in some cases, which may lead to the consideration of the possibility of both when either is discovered.

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

The initial diagnosis of spinal accessory neuropathy was only made after several weeks of symptomatology and was not considered until several weeks after the patient’s tendency to right upper extremity weakness was noted. At the time of initial diagnosis, palpable scapular winging and right shoulder droop were present. The diagnosis of spinal accessory neuropathy was initially suspected on the basis of induration along the incision site and a palpable cord within the right supraclavicular fossa. There was moderate atrophy of the right sternocleidomastoid and trapezius, with right shoulder drooping and minor right scapular winging.

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

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

Correspondence to: Dr George Woodward, Neurol-ogy Section (111), VA Medical Centre, Leaven-worth, Kansas 66048, USA. Telephone 001 913 682 2000 extension 2441; fax 001 913 758 4225.


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

We report the first case of extensive cerebral infarct in a young sportsman consuming high doses of MaHuang extract and creatine monohydrate for body building.

A 33 year old man had a severe aphasia on awakening in the morning of 23 January 1999. He did not complain of any other symptoms. He was referred to our department on 26 January 1999. He had a Wernicke aphasia with a slight right sided face and arm weakness and a right Babinski sign. His blood pressure was 140/60 and his pulse 54 per minute. Brain CT showed signs of extensive left middle cerebral artery infarct. Cervical ultrasound duplex scanning and cerebral angiography were normal. Cerebral CSF examination showed no abnormalities except for a patent foramen ovale.

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

Although a paradoxical embolism through a patent foramen ovale in this patient cannot be ruled out as he recently returned from a transatlantic air flight, there was no deep venous thrombosis and D-dimers were normal. However, ephedrine has an indirect sympathomimetic effect, which may cause further arteriovenous constriction in addition to other catecholaminergic effects. Both ischaemic and haemorrhagic stroke associated with ephedrine use have been reported.\textsuperscript{1} Acute myocardial infarction and acute psychosis have also been reported after taking ephedrine and other sympathomimetic drugs.\textsuperscript{1} Ephedrine and its metabolites are natural products that are used in non-prescription medicines for multiple uses. Ephedrine is contained in many products available over the counter, which contains ephedrine, is used among young sportsmen and sportswomen as an energy supplement in non-prescription tablets in some countries. Although no cardiac side effects have been reported with the use of creatine monohydrate, this compound, used in association with other drugs as energy supplement may have deleterious side effects. This may be particularly true when used at high doses in combination with sympathomimetic drugs as in our patient. Renal dysfunction has also been reported after oral creatine supplements. Our patient had a slight increase in creatine 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 BOUSSE
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 dysaesthesia of the upper quadrant of her face for 1 year. In addition she had intermittent ipsilateral headache. A left sided facial palsy and hypogeusia developed. When progressive hearing loss and persistent ipsilateral tinnitus occurred she sought medical advice. She was referred to our department for further treatment after a large tumour in the left cerebellopontine angle had been demonstrated by MRI. On admission, the left corneal reflex was absent. There was marked hypoaesthesia of the first two divisions of the left trigeminal nerve and a mild left facial palsy. There was also hypogeusia of the left half of the tongue. Speech was slightly dysarthric. During examination dystonic and choreic movements of the left facial muscles were seen. The dystonic grimacing increased when the patient was being observed. There were also intermittent jerky dystonic head movements with turning of the head to the left, associated with slight elevation of the left shoulder. The facial movement disorder was clearly different from hemifacial spasm. There were no tonic or clonic synchronous contractions of facial muscles and no signs of involuntary coactivation. The patient barely noted the dyskinesias. Audiometry showed a hearing threshold at 30 Db on the left side and lack of stapedius reflex on the left side. Oculovesotibular response to caloric stimulation was
decreased on the left side. Furthermore, there was mild left dysdiadochokinesia.

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

An MRI study showed a large gadolinium enhancing tumour within the left cerebellar pontine angle extending to the cavum Meckeli with marked displacement of the brainstem to the contralateral side (figure A and B). T2 weighted angiography showed a discrete blush of the tumour as typically seen in meningiomas. The tumour was totally removed by a combined transpetrosal supratentorial and infratentorial presigmoidal approach. The postoperative course was uneventful, and there were no new deficits. The facial palsy improved slightly as well as the trigeminal hypoparesis. 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 relationship is suggested also by the absence of a family history of movement disorders and the absence of previous exposure to neuroleptic medication. Hyperkinetic movement disorders due to tumours of the brainstem or of the posterior fossa have been reported only rarely. Asymmetric blepharospasm was recently found in a patient with an ipsilateral mesencephalic cyst. Acoustic neuroma was seen in patients with parietal neoplasm and cranial dystonia. Epileptic seizures and epidermoid tumours of the cerebellar pontine angle. Acoustic neuromas and anaplastic pontocerebellar glioma can be associated with facial myokymia and spastic parietic facial contracture.1 Also, cervical dystonia due to tumours of the cerebellopontine angle have been reported recently.1

The pathophysiological mechanisms responsible for dystonic movement disorders caused by structural or functional lesions of the brainstem are not fully understood. The possibility of denervation supersensitivity of cranial nerve nuclei has been proposed previously. Alternatively, enhanced excitability of brainstem interneurons has been suggested. The 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.2 We report on a patient in whom multiple cerebrovascular white matter lesions developed after taking dialysable leucocyte extract orally for facial myokymia and spastic paretic facial contracture.


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.3 The mechanisms of action of transfer factor are still far from clear; in vitro dialysable leucocyte extract increases macrophage activation and interleukin (IL) 1 production and enhances leucocyte chemotaxis and natural killer function. Transfer factor has been reported to stimulate the cell mediated antigen specific response in patients with various infections;4 therefore, treatment with transfer factor has been suggested in patients with selective deficits in cell mediated immunity such as in some refractory neoplasms and chronic infections. Moreover, it has been used in the treatment of uveitis.5 Administration of dialysable leucocyte extract has seemed to be free of hypersensitivity, long lasting side effects, or complications, except for transitory hyperpyrexia.

We report on a patient in whom multiple cerebral white matter lesions developed after taking dialysable leucocyte extract orally for facial myokymia and spastic paretic facial contracture. A 28 year old man was admitted to the hospital because of headache, mental confusion, and right hemiparesis. He had had recurrent bilateral uveitis from the age of 12 to 14 with right retinal detachment in the right eye. In January 1995 retinal vasculitis was diagnosed at fundoscopy and in July 1995 he started oral transfer factor as dialysable leucocyte extract twice a week. He complained of generalised weakness after the second dose and the referring symptoms developed after the third dose. Neurological examination on admission showed mental confusion and severe right spastic hemiparesis with Babinski’s sign. No fever or meningismus were present.

Laboratory examinations on admission showed a slight increase in total serum protein (8.4 g/l, normal 6.0–8.0 g/l, although the serum protein fraction was normal), antistreptolysin titres (355 UI/ml, normal<200 UI/ml), and anticardiolipin IgG (30 UI/ml, normal<40 UI/ml). Negative results were obtained for HIV, rubella, and herpes virus, CMV, Epstein-Barr virus, and JC virus in the CSF. All laboratory analyses were normal except for antistreptolysin tites (265 UI/ml). Two MR scans at 1 and 4 months after onset showed progressive reduction of lesions without contrast enhancement. A final MR scan 20 months after onset showed further regression of lesions without contrast enhancement but a new large lesion in the left occipital white matter, which showed moderate contrast enhancement. At present, after 5 years, the patient is in a good state of health and neurological examination and laboratory tests are normal.

The close temporal relation between assumption of dialysable leucocyte extract therapy and appearance of cerebral white matter lesions in our patient supports the possibility that the association of the two events might not be causal. Despite the absence of biopsy, we reasonably excluded

Correspondence to: Dr J K Krauss, Department of Neurosurgery, University Hospital, Klinikum Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany


Axial T1 weighted image after contrast administration showing multiple focal lesions in the periventricular white matter and left centrum semiovale exhibiting slight annular enhancement.
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.

The diagnostic 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.1 On the other hand, the fact that acute disseminated encephalitis may recur has been accepted and on the basis of the patient's clinical picture and CSF, we favoured such a diagnosis.

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

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

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

Neurological examination showed bilateral hyperreflexia, mild imprecision of fine finger movements, dysgraphaesthesia on sensory testing, and a manneristic gripping handshake. There were no extrapyramidal...
symptoms. His IQ score was in the low range (WASI-C=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 other's intentions. These two findings are reliably present in pervasive developmental disorders, in this IQ range. In addition, his performance on the Tower of Toronto test disclosed impaired performance in procedural learning. Psychiatric assessment showed scores above the cut off for autism according to the autism diagnostic interview (ADI), a standardised interview that requires specific training and those administering it to have a 0.90 reliability with other researchers. The subject was positive for the diagnosis of autism, being above cut off values in the three relevant areas of communication, social interactions, restricted interests, and repetitive behaviour. Nevertheless, he did not present delay in language acquisition or morphological atypicalities in language development, which corresponds to DSM-IV criteria for Asperger’s syndrome.

Brain CT showed dense calcium deposits in the basal ganglia, thalamus, cerebellar dentate nucleus, and orbitofrontal cortex, consistent with Fahr’s disease (figure). SPECT showed increased activity in basal ganglia relative to the cerebral cortex. A fine banded karyotype was normal. Serum calcium was 1.55 mM (normal 2.15–2.55 mM), phosphate 1.69 mM (normal 0.70–1.65 mM), calcium was 0.80 mM at pH 7.4 (normal 1.19–1.34 mM); urinary calcium was 0.8 mM (normal 2.5–6.3 mM). Serum parathyroid hormone was below 0.6 (normal 1.0–6.55 µU/L), and a nuclear scan of the parathyroid glands showed an absence of activity. With a combination of vitamin D3-calcium supplementation and cognitive-behavioural therapy, serum calcium, and phosphate concentrations normalised and his behaviour improved marginally.

Asperger’s syndrome is a subtype of pervasive developmental disorder of unknown aetiology. Evidence for involvement of specific brain regions in pervasive developmental disorder are scarce and inconclusive. Although the tempo-orbital region is the most often involved in pervasive developmental disorders, abnormal functioning of the frontal lobe is suspected from replicated findings of executive function deficits and from occasional findings of frontal hypometabolism or abnormal macroscopic brain morphology. Abnormal cell counts and morphology in the cerebellar hemispheres have also been reported, but the relation of these findings to autism is controversial.

Fahr’s disease consists of symmetric calcifications, located mainly in the basal forebrain and cerebellum, which are of various aetiologies. Cognitive and behavioural abnormalities may be present when calcifications occur early in development. A fortuitous association between pervasive developmental disorder and Fahr’s disease was found, given the paucity of published cases, is plausible in the presented patient. Nevertheless, our case suggests that abnormal phospho-calcium metabolism could produce an autistic syndrome when brain calcifications cause specific neuropsychological deficits, due to their localisation. For example, errors of social judgement may be related to calcifications of the orbitofrontal cortex, whereas dysfunction of frontal-basal ganglia circuits may contribute to repetitive and ritualistic activities. Additionally, developmental lesions of the basal ganglia and cerebellum may contribute to the abnormalities of sensory attention, procedural learning, and motor intention in this patient.

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

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, taphaceous gout, calcification of the posterior longitudinal ligament, synovial disease-like pigmented villonodular synovitis, and synovial chondromatosis. Hypertrophy of the atlantoaxial ligaments as a consequence of degenerative disease was recently recognised as an individual entity. Only five previous cases have been published. We add another case to the short series available in the literature, emphasising that as the cause of the spinal cord compression is amenable to surgical removal, symptomatic patients should be diagnosed and treated without delay.

A 66 year old woman presented with a rapid development of progressive spastic tetraparesis and an unremarkable medical history. There was no osteolysis or instability on plain cervical radiography and C.T. A bone scan with “Tc was unremarkable. Magnetic resonance imaging showed a retro-odontoid extradural mass that was homogeneous and isointense on T1 weighted signal, demonstrated 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 transtoral 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-inflamatory, 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.
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 reflex, were normal. The patient’s only complaints were left temporal headache and right hemihypaesthesia.

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

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

T2 weighted images 1 month later showed a more localised lesion in the same area. The coronal slices showed a high intensity lesion at the level of lower midbrain coinciding with the tentorium level, disclosed as a low line between the occipital lobe and the cerebellar hemisphere (figure). The neurological deficits almost disappeared 6 months later.

Somatosensory impairment including pain is one of the most common complaints among patients with craniocerebral 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.
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. Degeneration of certain cerebellar pathways is probably responsible for the loss of this dopaminergic innervation. Dopamine agonists could therefore be of potential interest in the treatment of toluene induced tremor. This hypothesis was explored in a recently described case, which showed remarkable clinical and iconographic similarities with that described by Miyagi et al: (a) long history of chronic toluene inhalation, (b) marked postural tremor, (c) progressive worsening of the symptoms despite abstinence from inhalant misuse, and (d) mild cerebral atrophy and marked low signal intensity in globus pallidi, thalami, red nuclei, and substantia nigrae on T2 weighted MRI. As our patient’s tremor was progressive, medical treatment with a dopamine agonist was considered. One particular agent (amantadine) caught our attention because it had proved successful in the treatment of postural tremor and ataxia of heredodegenerative disorders in which the dentatorubro-olivary system is affected. In addition, there is evidence that catecholaminergic pathways are also involved in this type of ataxias, supported by the idea of naming it a neurogenic form of ataxia. So, 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 after a month period.

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

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

We think that there are two problems with this study that should make the physician cautious about the factors identified by Nabbutt et al as a basis for a screening programme. The first is that this study was performed in a population that had been referred to a tertiary medical centre, and then had been further selected by virtue of having had at least 3 years tertiary centre follow up and needing two MR scans of the head. The prevalence of astrocytomas and risk factors, and hence the positive predictive value of any screening tool, in a general population of patients with tuberous sclerosis complex is likely to be different from those described in the highly selected group studied in this paper. The second problem is that the authors have made a potentially misleading decision to exclude more than half their study sample because they do not have lesions close to the foramen of Monroe. It is not certain that all SEGAs arise from lesions close to the foramen. They may arise in the fourth ventricle. Furthermore, the late presentation of many lesions in the lateral ventricles has, in the past, precluded accurate determination of their point of origin. A study of 24 of 60 patients who died or were treated with a Vim thalamotomy (in press).
“man-in-the-barrel” syndrome has even been suggested. It is probably difficult to differentiate it from progressive muscular atrophy (PMA). Some authors have said that PMA with late onset scapulothalamicus distribution (over 45 years of age) generally leads to ALS as a matter of course.1

Some of these patients have a long ALS clinical course, in that they usually preserve ambulatory ability, albeit with gait disorders, for many 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 (VFC, 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 deltoideus muscle atrophy. A meticulous study shows that there is an atrophy of the deltoideus muscle atrophy. A meticulous study shows that there is an atrophy of the deltoideus muscle atrophy. A meticulous study shows that there is an atrophy of the deltoideus muscle atrophy.

Atrophy and weakness of the infraespinaus and the supraespinaus, that act as an active ligament in scapulothoracic articulation, would explain the presence of subluxation of the shoulder joints in these patients.

Finally, we are in complete agreement that the presence of cervical spondylosis and ALS can cause difficulty in diagnosis. The problem lies in the fact that cervical spondylosis is a common condition. It is found in 85.3% of men and 80.7% of women over the age of 55.2 The faster progressive deterioration of the symptoms, the appearance of bulbar signs, and the absence of sensory symptoms and signs would favor the diagnosis of ALS.3

Correspondence to: Correspondence to: Dr Josef Garmez, Servicio de Neurología, Hospital General Universitari Vall d’Hebron, Passeig Vall d’Hebron 119–135, 08035 Barcelona. Spain. email: 127841gc@comb.es


Sasaki replied: We thank Garmez et al for their interest in our article concerning the atypical form of amyotrophic lateral sclerosis.4

Over many years, several researchers have recognized this peculiar distribution of muscle atrophy in clinical practice. The clinical manifestations consist of the muscular atrophy confined to the shoulder girdle and the arms (proximally dominant), absence of deep tendon reflex in the arms, almost normal deep tendon reflex in the legs, and subluxation of the shoulder joints. Some patients progress to bulbar involvement.4 By contrast with clinical awareness of this phenomenon, pathological confirmation had been made in only 2 of 10 patients reported by Vulpian in 1886 and known in Japan by 1930. The faster progressive deterioration of the symptoms, the appearance of bulbar signs, and the absence of sensory symptoms and signs would favor the diagnosis of ALS.4

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Isolated dysarthria

We read with interest the article by Urban et al. Using transcranial magnetic stimulation, the authors demonstrated electrophysiologically evidence for a central monophasic of the tongue in patients with isolated dysarthria from stroke.5 As in their patients transcranial magnetic stimulation induced absent or delayed corticomedullar responses at the tongue, the authors ascribed isolated dysarthria to interruption of the corticomedullar pathway, resulting in functional impairment of 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 this ascending and descending pathway.6

To assess corticopontocerebellar tract function, Urban et al investigated cerebellar blood flow in patients with isolated dysarthria using HMPAO-SPECT.7 This article included that the corticopontocerebellar tract is preserved in isolated dysarthria because of no evidence for cerebellar diaschisis on SPECT. Their SPECT findings on cerebellar blood flow were similar to our results. However, we wonder whether cerebral cortical blood flow was preserved in their patients, because our SPECT study suggested frontal cortical dysfunction as an underlying mechanism of isolated dysarthria. Languagelapse was evident in three of seven patients reported by Urban et al and in two of 12 by us. This indicates that isolated dysarthria originates in incoordination of multiple organs necessary for speech 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 this ascending and descending pathway.6

At last, we think Garmez et al for their interest in our article concerning the atypical form of amyotrophic lateral sclerosis.4


Urban et al reply:

Okuda et al draw attention to their article on pure dysarthria in Stroke which we read with much interest. They refer to 12 patients with pure dysarthria, 11 of whom showed multiple bilateral infarctions involving the internal capsule and corona radiata. The main difference to our series of seven patients is the multiple involvement of the brain. We think that our single lesion allows us to propose an approach to correlate lesion topography with impaired function. The findings of Okuda et al are in line with our conclusion that interruption of the corticolumbar pathway is critical to the pathogenesis of dysarthria of extracerebellar origin. Obviously, impairment of the corticolumbar tract of one hemisphere by a single small lesion is an adequate condition for dysarthria. The patients of Okuda et al had more severe vascular disorder of the brain than our patients as can be concluded from the multiple infarctions. Thus, the bilateral frontal cortical hypoperfusion as disclosed by SPECT in the series of Okuda et al may be due to infarction in other parts of the brain compared with the lesion causing pure dysarthria.

P P Urban
S Wicht
H CH Hopp
Department of Neurology, University of Mainz, Langenbeckstrasse 1, D55101 Mainz, Germany

S Fleischer
Department of Communication Disorders
O Nickel
Department of Nuclear Medicine

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 are due to different patient selection as they included patients with early stage Huntington’s disease to “study the pathophysiology of chorea unaffected by other disorders movement.” They postulated that our cases, because of the reported correlation with a dyskinetic rating scale, had a more advanced stage of the disease possibly with coexisting dystonia or rigidity. These assertions deserve some comments.

The mean disease duration of our nine patients with Huntington’s disease was 6.2 (4.1) years which is about 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, with the Unified Huntington’s disease rating scale, and none presented dystonia, rigidity, or any other additional movement disorder. In this regard, however, it should be pointed out that bradykinesia is often associated with chorea in patients with Huntington’s disease and may even precede the appearance of choreic dyskinesias.1 Chorea itself is often reduced in the more advanced Huntington’s disease stages.1 It is unlikely, therefore, that any neurophysiological approach can test purely chorea even in the early Huntington’s disease stages. In addition, different mechanisms are involved in Huntington’s disease and other choreas as suggested by the lack of impairment of somatosensory evoked responses and long latency stretch reflexes in the second.2

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 whom already reported,3 with positive DNA testing but completely asymptomatic.

The discrepancies between the two studies are more likely to be explained, at least in part, by some methodological differences. For instance, the amplitude of the control response was larger in our set (approximately 1.0 mV compared with 0.5 mV in the study of Hanajima et al). This may induce a different sensitivity of the test, and the amount of intracortical inhibition in our normal controls is greater (see also1) than in the study of Hanajima et al.

When interpreting the results of studies with paired transcranial magnetic stimulation pathophysiologically it should be kept in mind that similar changes of intracortical inhibition have been shown in patients with various movement disorders (focal dystonia, myoclonus, parkinsonism, restless legs syndrome, Tourette’s disorder), but also in different diseases such as amyotrophic lateral sclerosis.4 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.

G Abbruzzese
R Marchese
C Trompetto
Department of Neurological Sciences and Vision, Movement Disorders Clinic, University of Genoa, Via De Toni 5, I-16132 Genoa, Italy


The authors reply:

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

The discrepancy between the two studies2 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 stimulation. Therefore, we used the intensities of the conditioning stimulus before we confirmed inhibition in studies of patients.3 We used an intensity of 5% less than the active threshold as a conditioning stimulus, and a facilitatory effect must often superimpose on the intracortical inhibition. This makes the interpretation difficult. Was the intensity of 80% of the resting threshold or 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 study.

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 dependent on FV(t) as well as on the vascular tone. 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. Whichver 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 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 (ABP1, ABPd), respectively, it follows that systolic and diastolic FVs (FvS, FvD) should be equal to (ABP1−CCP)/CVR and (ABPd−CCP)/CVR, respectively. However, it is well known that the vascular resistance valid for the static pressure/flow connection (CVR), concerning mean pressures and flows) is different from and is in general much higher than resistances determining dynamic pressure/flow relations (CVR) as in the case of pulsatile pressure. Therefore, equation 1 cannot be applied to describe dynamic flow. This can be best illustrated using the frequency domain approach (ABP=mean pressure; FV=mean flow velocity; AS=amplitude of the pulsatile pressure wave; F1=amplitude of the pulsatile flow wave):

FV = (ABP−CCP)/CVR (2)

F1 = A1/CVR (3)

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

CCP2 = ABP−A1/F1 (4)

leads to:

CCP2 = ABP−CVR1/CVR0 × (ABP−CCP) = ABP−CVR1/CVR0 + CVR1/CVR0 (5)

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

CCP2 = 0.5ABP−0.5CCP (6)

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

The second criticism concerns the correlation of the calculated CCP2 values with mean ABP found by the authors (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 CCP2 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 vasodilatation. However, the relative contribution of both effects is critical for the limit of CCP.

Finally, I would be interested in the authors’ explanation of negative diastolic flow values as seen in Doppler spectra of arteries with a high vascular resistance (peripheral arteries, middle cerebral artery during strong hypcapnia). In the case of ABP1>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 flow is more accurately given by cerebral perfusion pressure (CPP = ABP−ICP) than by ABP-CPP. Therefore, equation 2 changes to:

FV = (ABP−CPP)/CVR (6)

and equation 5 to CCP2 = ABP−(1−CVR1/CVR0)+CVR1/CVR0 (7)

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

ROLF R DIEHL
Department of Neurology, Krupp Hospital, Alfeld-Krupp-Straße, 45117 Essen, Germany


Czosnyka et al reply:

We thank Diethl for his very interesting letter provoking us some mathematical considerations about cerebral haemodynamics. We need to emphasise that our primary intention1 was to investigate Burton’s hypothesis2 in patients with head injury3 that critical closing pressure (CCP) may be represented by a sum of intracranial pressure (ICP) and the tension in the arterial walls.

CCP=ICP+active tension of arterial walls

Asall proposed the mathematical formula taken for calculations:

CCP1 = ABP−ABPPp/FvPPp×FVpp−FvPP (5)

(where ABP and FV are mean values of arterial pressure and MCA flow velocity, ABPP and FVPPp are systemic values, ABPP and FvPPp are peak to peak amplitudes). A graphical interpretation of this formula has been given in fig 1. CCP1 is an x intercept point of linear regression between subsequent systolic and diastolic values recorded within 6 second intervals of flow velocity (along y axis) and arterial pressure (along x axis).

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

CCP2 = ABP−A1/F1×FV (6)

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

First of all we cannot see how equation (1) from Diethl’s letter can be derived from any of our formulae. Everyone who has tried to plot momentary values from ABP pulse waveform against momentary values of FV waveform knows that it never plots a straight line (equation (1) implies), because the “clouds” of systolic and diastolic values of ABP and FV waveforms (fig 1 in1) one can rather see an ellipsoidal shape which is very seldom regular enough to be approximated by a straight section. Therefore, equation (1) in Diethl’s letter is not correct. In fact, CVR is a frequency dependent variable (represents vascular impedance) and if a linear theory can be applied, division in (1) should be substituted by a convolution with an inverse Fourier transform of “cerebrovascular admittance”.

Definition of CVR0 as FV/ABP−CCP is completely artificial and lacks a physiological basis. It is rather taken from the geometrical interpretation of figure 1 in1. In our material equivalent of parameter CVR0 (as defined by Diehl) is 1.007 (SD 0.31) and CVR1 0.972 (SD 0.29), the difference was not statistically significant. Therefore, the suggestion that the CVR1/CVR0 ratio is 0.5 is not correct. Real CVR0 should be calculated as (ABP−ICP)/FV. We fully agree that equation (5) proposed by Diehl is “useless for valid CCP calculation”. We have not used it and have never suggested anyone could do so.

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

The final issue concerning negative flow velocity is a trap Diethl has prepared for himself. We never suggested that any factor interpretable as cerebrovascular resistance (CVR0 or CVR1) should be involved in the concept of critical closing pressure. From the definition, closing is a strongly non-linear phenomenon, therefore applying linear theory here is very
risks. How risky—we can see from Dieth's let-
ter. 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 understanding as a combination of ABP and ICP remains. Whether it simplifies our understanding as a combination of ABP and ICP lies. A recent anatomical study also showed that the cortical-subthalamic nucleus con-
nection is somatotopically segregated, so that fibres from the supplementary motor area project to the most medial portion and fibres from the primary and premotor areas termi-
nate in the lateral region of the subthalamic nucleus. All this heterogeneity may have pathophysiologieal relevance, one aspect of which could be the findings in the patient reported by Figueiras-Mendez et al. However, before the findings of this case may be used to sustain a role 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-
trode: (1) Stimulation of the subthalamic nucleus in Parkinson's disease has been asso-
ciated with the production of dyskinesias only recently reduced in levodopa intake. Moreover, Benabid et al who pioneered this technique, consider the induction of dyskine-
sias by high frequency stimulation of the sub-
thalamic nucleus as a good indicator of a very positive response to the stimulation. Stroking to the thalamus from the globus pallidum internum are placed dorsocaudally to the subthalamic nucleus and could be blocked by high frequency stimulation. (3) When the record-
ing electrodes are in the subthalamic nucleus as a good indicator of a very high activity is observed to the subthalamic nucleus in sagittal planes 11 mm or less, neuronal activity is characterised by action potentials of large amplitudes (0.5–1 mV) with a low background activity, tonically firing neurons, and absent sensori-

tomotor responses (“driving”). All these char-
acteristics seem to be present in the patient discussed here. Neuronal activity in the sensorimotor nucleus of the subthalamic nucleus is different from the above but on occasions the distinction may not be easy.

Accordingly, it is very important to doc-
ument in more detail the findings in the case of Figueiras-Mendez et al. Ideally, we would like to see the trajectory and length of the differ-
ent recording tracks, the effects of micro-

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

Recognition of the electrical activity of the subtha-
lamic nucleus is a key point in the diagnostic criteria: (a) high frequency discharge (25 Hz or higher) within the nucleus+; (b) a tonic (regular), phasic (irregular) or a rhythmic pat-
ttern 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 analysis of the EMG correlations 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, (e) the activity of the cells below the subthalamic nucleus. The sub-
thalamus and zona incerta with proper characteristics; (f) a change in the back-
ground basal noise when entering the subtha-
lamic nucleus. A higher activity is observed; (g) activity is altered by lesions in the subtha-
lamic nucleus; (h) a lower background noise level; (h) 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. All these points were fulfilled by the patient reported.

Considering the questions in the letter by Obeso et al, we make the following com-
ments: (a) Action potentials of levodopa-induced dyskinesias are well known and recorded in the subthalamic nucleus. A more detailed analysis of the recorded potentials is needed before the distinction can be made. (b) The relationship between the subthalamic nucleus and the basal ganglia has been well described. (c) The distinction between the subthalamic nucleus and the basal ganglia has been well described. (d) The relationship between the subthalamic nucleus and the basal ganglia has been well described. (e) The distinction between the subthalamic nucleus and the basal ganglia has been well described. (f) The relationship between the subthalamic nucleus and the basal ganglia has been well described.
Nitric oxide in acute ischaemic stroke

The pivotal role of nitric oxide (NO) in cerebral ischaemia has been elegantly highlighted in the recent editorial by O'Mahony and Kendall. Although studies of neuroprotective agents have been largely disappointing, pharmacological manipulation of NO may represent a novel means of protecting the brain from ischaemic insult. One area not discussed in the recent article is the neuroprotective effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or “statins” in cerebral ischaemia. Preliminary studies have shown that statins modulate brain nitric oxide synthase activity and are neuroprotective in a neuroprotective manner. Data from a murine model of ischaemic stroke demonstrate that prophylactic statin therapy reduces infarct size by about 30%, and improves neurological outcome in normocholesterolaemic animals. In this investigation, statin therapy directly upregulated endothelial NO in the brain without altering expression of neuronal NO. Recent findings also suggest that statin therapy influences the activity of inducible NO. Lovastatin has been shown to inhibit cytokine mediated upregulation of inducible NO and production of NO in rat astrocytes and macrophages, and this inhibition may represent a means of suppressing inflammatory responses that accompany ischaemia. Most interestingly, these preliminary findings suggest that statin therapy may modify the friendly and unfriendly faces of brain NO in a synergistically neuroprotective manner. These and other vascular effects of statins in cerebral ischaemia are potentially of great importance in human neuroprotection and ongoing studies such as the The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study will help clarify their role in human cerebrovascular disease.

CARL J VAUGHAN
Division of Cardiology, Department of Medicine, Will 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, The University of Pennsylvania, Philadelphia, Pennsylvania, USA
Correspondence to: Dr Carl Vaughan email evaughan@nihs.med.cornell.edu


O’Mahony replies:
The comments of Vaughan and Delanty draw attention to the evidence that statin therapy may be neuroprotective. 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) study will help clarify their role in human cerebrovascular disease.

DENIS O’MAHONY
Clinical Investigation Unit, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, UK

BOOK REVIEWS


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

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

The book opens with a highly accessible chapter on immunology of the mammalian host system. There follows a chapter that integrates the neurobiology of multiple sclerosis with contemporary issues of aetiology, cell injury, and repair. Next, a chapter on inflammatory demyelinating disease and experimental 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

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 (Rösler et al). I found the review by Reisberg et al on ontogenetic models in the understanding of the management of Alzheimer’s disease particularly interesting. However, the papers of original research are of more limited interest to the general reader. Although, as mentioned, the quality of illustrations is good, there is some variability in the definition of abbreviations and occasional lapses into other European languages.

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

JON SUSSMAN

CLARE GALTON


Volume nine of the Current Issues in Neurodegenerative Diseases 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 within any illustration. Each contribution to 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 contribution of white matter changes on neuroimaging to dementia, and finally a short section examining practical questions such as the management of stroke in patients with dementia.

Although common somewhere in 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. Still, the 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 enchainment 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, involving observation, inference, motive, and consequence in a fashion that informs future action. Our experience of the world is constructed around such narratives. They define us as individuals, family members, professionals, and cultural groups.

This book is a series of essays on psychotherapy, psychiatry, and also medicine that sees the awareness and use of narrative in clinical practice as a construct that can both...
deliver effective care as well as act as a conceptual bridge between the different disciplines. One of the great pleasures of being a doctor has always been listening to patient’s stories, but the editors of this book fear that this essential art can be overtaken by dull scientific pragmatism. Referring to the opening chapter, writes a lucid and well reasoned account of the need to search for and maintain narrative meaning in treating psychosis. This approach, examining effect to both patients and professionals of identifying individuals by their illness as in schizophrenia. Every psychiatric library should buy this book for this paper alone, which should be required reading for all psychiatrists.

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


In a small accessible and easily digestible volume, the authors address a clinically important field. Faced with slim evidence on which to base clinical recommendations, they acknowledge that their very useful management advice “has often had to be based on practical clinical experience rather than the results of clinical trials or formal research.” This disclaimer seems to have allowed them to mix evidence and opinion, limit references, and confuse the reader regarding the level of evidence. A pity, as the authors, with special expertise in this important area, have made a good start in putting together different aspects of the care of the woman with epilepsy in a practical book that is of direct interest and relevance to neurologists, obstetricians, general practitioners, psychiatric specialists, and trained midwives. Moving on from the general to the particular, the text, although expansive in parts, glosses over some important points. Examples include (a) which oral vitamin K preparations are considered safe in pregnancy (phymenadione), (b) differential efficacy of various antiepileptic drugs in different syndromes versus side effect and teratogenicity profile, (c) more information on the limitation of available evidence to support the statement “no monotherapy human abnormality reported” with certain new antiepileptic drugs in pregnancy, (d) the need to consider women with a history of malformations in their family, (e) more information on the limitations of available evidence to support the statement “no monotherapy human abnormality reported” with certain new antiepileptic drugs in pregnancy, (f) to consider the use of vitamin K preparations in women with a history of malformations in their family, (g) time to closure of the neural tube (different from the 21-56 days they quote as the “most sensitive time of the fetus to the induction of malformations by exogenous agents.”).

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

LINA NASHEF


Childhood Epilepsies and Brain Development is the fruit of a symposium held in 1997 to try and bridge the chasm between those working in the clinic or at the bedside and those in the laboratory. Both groups must collaborate and communicate to improve the management of children (and older patients) with epilepsy. The book is essentially a collection of monographs of heterogeneous content and style and the result, perhaps not surprisingly, is that some of the component parts are better than the sum. The clinically oriented section will clearly be of particular interest to those who treat children and their families. The chapters on infantile spasms and Lennox-Gastaut syndrome are informative and provide some new but speculative insights into the pathogenesis of spasms. However, it was surprising that severe myoclonic epilepsy of infancy did not mer it a specific chapter in view of the unique electro-clinical evolution and natural history of this syndrome. The crucial issue of the cognitive and behavioural sequelae of early and frequent seizures on the immature brain, which is probably of most concern to both clinicians and families, is succinctly addressed in two chapters—although a clear and consistent cause and effect relation remains to be established. The chapters covering basic neurophysiology, neurochemistry, and neuropathology, are erudite and fascinating but at times are barely comprehensible. 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 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 due to a prolonged editorial atypical apathy, and although this mitigates against it becoming a well thumbed reference text, the book is an erudite addition to the clinical literature. RICHARD E APPLTON


The Maudsley prescribing guidelines are produced each year for a local readership, but this, the fifth edition, is the first to go public. The authors and principal contributors, a mixture of psychiatrists and psychologists with an interest and background in clinical psychopharmacology, are to be complimented on producing a guide of manageable size and ready accessibility. The book is divided into sections dealing with the treatment of broad groups of clinical disorders—for example, psychosis—special patient populations—for example, elderly people, with further sections on the management of emergencies and the adverse effects of psychotropic drugs. Much of the information is laid out in tabular form. It could become an indispensable resource for a busy on call senior house officer (the dimensions would fit comfortably into the pocket of a clinical white coat, were they still to be worn) but more senior clinicians will find plenty of use for it in the clinic. It does not aim at great erudition, but provides a useful list of references.

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

BRIAN TOONE


Unsurprisingly, given the psychopharmacological expertise of the editors, this book is innovative and comprehensive. The 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 but is not one that I would recommend because some aspects of the practical management of violence are missing—for example, a documented risk-benefit analysis, good failsafe communication, or deciding when to detain. One of the last chapters is a very good account of the management of hyperactivity in childhood, with good practical advice on the use of 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