LETTERS TO THE EDITOR

Postictal psychosis related regional cerebral hyperperfusion

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

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 Antiepileptic drugs were withdrawn to facilitate seizure recording.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

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

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

Interictal SPECT and SPECT performed during postictal psychosis. (Top) A SPECT study of patient 1 showing areas of relative hyperperfusion over the right temporal neocortex (red arrows) and the left basal ganglia (blue and yellow arrows) during postictal psychosis. (Bottom) SPECT study of patient 2 showing areas of hyperperfusion over the right temporal neocortex and the left basal ganglia. Arrows indicate areas of hyperperfusion.
started after the cerebral SPECT. His psychotic symptoms resolved 2 weeks later with full recovery.

Cerebral SPECT performed during the interictal period (IP) and during postictal psychosis (PP) were analysed. Visual and area asymmetry scores were calculated. 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 + ROI contralateral)×100%. We set an arbitrary change of ASI >100% to be significant. As there were only two patients, statistically 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% (+6.46476 to -1.65289); over the right LT was +116.7% (1.07927 to 12.55764); and over the left BG was +206.8% (2.07373 to 2.21574). Quantitative analysis for patient 2 showed changes of ASI during IP and PP over right MT was +3.8% (13.14217 to 12.64156); over right LT was +178.6% (10.4606 to 18.70057); and over left BG was +155.9% (5.85556 to 3.27522).

Postictal psychosis is a distinct clinical event associated with temporal lobe epilepsy. The diagnosis of postictal psychosis requires a close temporal relation between bouts of complex partial seizures and the onset of psychosis. The psychosis usually develops after a clinical seizure. Partial seizures were usually precipitated by abrupt withdrawal of antiepileptic drugs. The cluster occurs in patients with poor drug compliance or during video EEG telemetry studies when antiepileptic drugs are withdrawn purposefully. The clinical course of postictal psychosis is usually benign and unpredictable.1 In our patients, the duration of psychotic disturbances lasted from 2 to 7 days, which is in keeping with the good prognosis. Antipsychotic drugs, such as haloperidol and fluphenazine are usually prescribed. The underlying mechanism of postictal psychosis is unknown. Postictal cerebral hypofunction has been postulated as an analogue to Todd’s paralysis after seizure.1,2 However, the presence of increased rCBF during postictal psychosis, may suggest an alternative explanation exerted by ictal SPECT has been shown to be highly sensitive and specific in demonstrating seizure foci.3 To conclude, our results are contradictory to the hyperfusion theory of Todd’s paralysis in postictal psychosis. We think that these 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.


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.9,10 Previous research from this laboratory disclosed that peculiar isoforms of fibronectin (FN) and tenasin (TN) typically occur in fetal and neoplastic tissues. These isoforms are a blend of structurally different glycoproteins that result from alternative splicing of the primary transcript and are mainly expressed in the extracellular matrix. Their expression is undetectable in normal adult tissues, with the exception of the vessels in the regenerating endometrium. To gain further insight into the pathobiology of the AVMs the present report sought to ascertain whether these lesions also express oncofetal FN and TN isoforms.

Tissue samples were obtained after neurosurgical excisions of ruptured AVMs. All 10 patients had experienced an intracerebral haemorrhage as the first clinical manifestation of their disease. There was no drug history before bleeding. Control specimen from two right gyri recti and one cerebellar tonsil were obtained, respectively, from operations for ruptured aneurysms of the anterior communicating artery or for Arnold Chiari disease.

Immunohistochemical evaluations were performed on 5 µm thick cryostat sections using a protocol reported previously.9 Owing to the limited amount of available material, only in a few cases was some fresh tissue retained to allow western blots. Distribution of FN and TN isoforms was investigated using three monoclonal antibodies (mAbs) or two Ab fragments, obtained from display technology, respectively. These Abs, prepared in our laboratory, were found to work on fresh frozen material. According to the previous characterisations the BC-1 mAb and the TN-11 Ab fragments are specific for isoforms occurring almost exclusively in fetal tissues and in tumours, with the recognised TN isoform being typically associated with anaplastic gliomas (table). The antibodies were blocked using the specific antigens. The antisera were recombinant protein containing the epitope produced in E Coli. For the mAb BC-1 we used the recombinant protein containing the type-III repeats 7B–8–9. For the mAb IST-4 we used the recombinant protein containing the type-III repeats 2–8. For the recombinant antibodies TN-11 and TN-12 the recombinant type-III repeat C and the recombinant fragment containing the BG-1 were used, respectively.

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 of BC-1 mAb was retained to allow western blots. Distribution of the isoform (s) Widespread Widespread Absent in adult tissues Present in the vascular wall and the matrix of fetal tissues and tumours

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

<table>
<thead>
<tr>
<th>Anti-FN mAb</th>
<th>Anti-TN Ab fragments</th>
<th>IST-4</th>
<th>IST-9</th>
<th>BC-1</th>
<th>TN-12</th>
<th>TN-11</th>
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<tr>
<td><strong>Recognised isoforms</strong></td>
<td><strong>Total FN</strong></td>
<td><strong>Isologs containing the ED-A sequence</strong></td>
<td><strong>Isolog containing the ED-B sequence</strong></td>
<td><strong>Total TN</strong></td>
<td><strong>Type III repeat C Isoform</strong></td>
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</tr>
<tr>
<td>Distribution of the isoform (s)</td>
<td>Widespread</td>
<td>Widespread</td>
<td>Absent in adult tissues (with the exception of the regenerating endometrium)</td>
<td>Present in the vascular wall and the matrix of fetal tissues and tumours</td>
<td>Widespread</td>
<td>Absent in adult tissues</td>
</tr>
</tbody>
</table>

6 The diagnosis of postictal psychosis requires a close temporal relation between bouts of complex partial seizures and the onset of psychosis. The psychosis usually develops after a clinical seizure. Partial seizures were usually precipitated by abrupt withdrawal of antiepileptic drugs. The cluster occurs in patients with poor drug compliance or during video EEG telemetry studies when antiepileptic drugs are withdrawn purposefully. The clinical course of postictal psychosis is usually benign and unpredictable. In our patients, the duration of psychotic disturbances lasted from 2 to 7 days, which is in keeping with the good prognosis. Antipsychotic drugs, such as haloperidol and fluphenazine are usually prescribed. The underlying mechanism of postictal psychosis is unknown. Postictal cerebral hypofunction has been postulated as an analogue to Todd’s paralysis after seizure. However, the presence of increased rCBF during postictal psychosis, may suggest an alternative explanation exerted by ictal SPECT has been shown to be highly sensitive and specific in demonstrating seizure foci. To conclude, our results are contradictory to the hyperfusion theory of Todd’s paralysis in postictal psychosis. We think that these 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.

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

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

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

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

The present findings indicate that a specific receptor upregulated in glioblastomas, by contrast with the neoplastic angiogenesis, is an endothelial cell-specific receptor tyrosine kinase is upregulated in the vasculature of arteriovenous malformations. This finding suggests that an inflammatory process is responsible for the cerebral dysfunction. In the absence of pathological data, the evidence for a specific pathogenetic mechanism is largely circumstantial. A small vessel vasculitis and immune complex deposition have both been suggested.

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

A 63 year old market stallholder without medical or psychiatric history was brought to a local psychiatric hospital by the police. His business had been in decline for several months, and his family had noticed uncharacteristic emotional liability. In the weeks preceding admission he had experienced delusions and hallucinations, and exhibited uncharacteristic behaviour. He had reported a vision of the crucifixion, and hearing the voice of his dead mother. He claimed that his business was occupied by the devil, drove around aimlessly in his car, and appeared constantly fearful and withdrawn. On the day of admission he had made a bonfire in the garden and burned his wife’s clothes, family photographs, furniture, and business papers. When his wife and son tried to intervene he...
became aggressive and threatened them with a saw. The general practitioner was called and subsequently referred the patient to a new psychiatrist and a severe depressive illness. Police assistance was requested because of the patient's continuing violent behaviour.

On admission he was unkept 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 errors, suggesting a predominantly “dys executive” pattern. CT and EEG were both normal, and SPECT disclosed widespread perfusion deficits, per- ticularly in the posterior temporal lobes. It is of note that, whereas his name- ing ability had improved, performance on frontal executive tasks remained impaired. The appearance of the follow up SPECT dif-

<table>
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<tr>
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<tr>
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<td>VDLR</td>
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<tr>
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<tr>
<td>WAIS-R (performance)</td>
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<tr>
<td>Digit span forwards (5)</td>
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<td>6</td>
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<tr>
<td>Rey-Osterreith complex figure (recall) (36)</td>
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<td>24</td>
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<tr>
<td>Not tested</td>
<td>75%</td>
<td></td>
</tr>
</tbody>
</table>

P J DE VRIES

N HUNT

University of Cambridge Department of Psychiatry, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK

A CRAWFORD

J R HODGES

MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 2EF, UK

K BALAN

Department of Nuclear Medicine, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK

Correspondence to: Dr P Garrard, University of Cambridge Neurology Unit, Box 165, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK

e-mail garrard@cnbc.cmu.edu


Alien hand sign in Creutzfeldt-Jakob disease

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

Creutzfeldt-Jakob disease, one of the human prion diseases, is characterised by rapidly progressive mental and motor deterioration.1 Involuntary movements occur in above 90% of the patients in the course of the disease, the most common being myoclonus.1 Other movement disorders range from tremor to chorea and dystonia, and hemiballism.2 We report on a patient with CJD who presented with an alien hand.

Alien hand is a rare and striking phenomenon defined as “a patient’s failure to recog- nise the action of one of his hands as his own”.3 One of the patient’s hands acts as a stranger to the body and is uncooperative. Thus, there is loss of feeling of ownership but not loss of sen- sation in the affected hand. Originally de- scribed in callosal tumours,4 the aetiology of alien hand also includes surgical callosotomy,5 infarction of the medial frontal cortex, occipi- tofrontal lobe, and thalamic infection,6 and corticobasal degeneration.7 8

A 70 year old, right handed Jewish man born in Argentina, living in Israel for the past 20 years, was admitted to the Neurology Department. Until a month prior to admission, he was apparently healthy and helped in the accounting office of the village where he lived. His neurological illness had presented insidiously during the past month with the sudden onset of gait and fine tremor, and axial dystonia.2 He also manifested behavioural changes, became aggressive, and had visual hallucinations, perceiving insects and mice moving through his visual field. Often, he expressed his fear from seeing that the "ceiling was
falling over him”. His wife mentioned bizarre, useless movements of his left hand which were present from the beginning of the disease. On admission, he was awake, bradyphrenic, and partially collaborative. His converse, hemiakinesia, disrupted by hallucinations. The affect was sad and he had partial insight for his mental dysfunction. He was disoriented for time, place, and situation. He could understand speech and was able to follow actions instructions involving two consecutive components. Naming was preserved. Prominent dysphasia and dyscalculia were noticed. Immediate recall and short term memory were severely disturbed, whereas long term memory, especially for personal life events, was relatively spared. Abstract thinking was severely affected. Bimanual movements, such as clapping, were extremely difficult.

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

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

The laboratory data including blood chemistry, hematological, and sedimentation rate were normal, as were folic acid, vitamin B12 concentrations, and thyroid function. Vene-

deal disease research laboratory and HIV tests were negative. The cerebrospinal fluid had normal content. Brain CT showed mild cerebral atrophy. An EEG showed severe dif-
fuse slowing at admission. Within a week, repeated EEGs showed triphasic waves with a periodic pattern of 1-1.5 Hz. During the next 2 weeks, the patient developed myoclonic jerks. Severe dysphasia and cognitive decline were accompanied by con-
fusion and aggression. He became grossly ataxic, and unable to walk and perform any of his daily activities even with help. Transferred to a chronic care hospital, he died few weeks later. Postmortem examination was not allowed.

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

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

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

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

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ment of Physiolo-

gy, University of California, Los Angeles, USA.

R INZELBERG
P NISPEANU
S C BLUMEN
R L CARASO
Department of Neurology, Hillel Yaffe Medical Center, Hadera, Israel

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


3 Broon S, Jedynak CP. Troubles du transfert interhemisphérique. A propos de trois observa-


8 MacGowan DJL, Delanty N, Petito F, et al. Isolated myoclonic alien hand as the sole presen-


10 Barclay CL, Bergeron C, Lang AE. Arm levita-

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 Gastro-

entrology and Nutrition (ESPAG) criteria. Since then she was on a strict gluten free diet and was asymptomatic until the age of 10 years when severe diarrhea, vomiting, and abdominal pain manifested 6 days after the intake of corn flakes erroneously thought to be gluten free. No previous infections had been noticed. One week after the onset of these symptoms she experienced acute weakness and pins and needles sensation confined to her legs. At that time her parents stopped her intake of corn flakes on the suspicion that these were responsible for the symptoms. Despite this, symptoms worsened during the next 2 days, confining her to bed.

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

Laboratory investigations showed a white cell count of 9300/mm3. The results of the following investigations were within the normal limits: haemogram, erythrocyte sedi-
mement rate, serum urea, nitrogen, electrolytes, creatinine, glucose, transaminase, bilirubin, immunoglobulins (Igs), lead, iron, copper, urinalysis, urinary porphyrin, folic acid, and vitamins A, B12, B6, and E. Anti- bodies to Campylobacter jejuni, neurotropic and anti-cereals, anti-ganglioside, IgA and IgG antibodies, specific or non-specific organ autoantibodies, IgA and IgG antiglia-
din antibodies (AGAs), IgA antiendomysium antibodies (EMA), and IgA anticytaculum antibodies (ARA), assessed by enzyme linked immunoabsorbent assay (ELISA) and im-
munofluorescence (IF) were also negative. Lumbar puncture was not performed. Anti-

bodies against gangliosides GM1 and GQ1b, myelin associated glycoprotein and myelin

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basic protein were not tested. Nerve conduc-
tivity studies were consistent with a predomi-
nately motor demyelinating peripheral neu-
ropathy (table). Her symptoms improved
spontaneously and she was discharged home
after 2 weeks. For 2 years she was asympto-
tic on a gluten free diet. Two weeks later, due
to persisting gastrointestinal symptoms, her
parents excluded the bread from her diet.
After 2 further weeks, while the abdominal
pain was gradually improving, she
had a new episode of acute weakness in the
lower limbs and sensory abnormalities in-
cluding burning 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 haemoglobin 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 asayed
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 brain 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,
occuring within weeks.

The present case, however, differs clinically
from those with neurological involvement pre-
viously reported. In the paediatric age group,
in fact, neurological complications of celiac
disease are rarely encountered and are mostly
cofined 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.²

In both episodes in the present case neuro-
physiology was strongly supportive of a
demyelinating peripheral neuropathy, which is
most commonly attributed to a direct
immuned mediated attack to the myelin. By
contrast, wallerian and axonal 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 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
MORIA FINOCCHIARO
ENZO PARANO
PIERO PAVONE
Division of Paediatric Neurology, Department of Paediatrics, University of Catania
Catania, Italy

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Frontal release signs in older people with peripheral vascular disease

A growing body of research examining neurological aspects of clinically “silent” cerebrovascular disease suggests that neurologi-
cal signs indicative of generalised organic brain damage may occur in the absence of completed stroke.¹ These soft signs include primitive reflexes (frontal release signs), re-
representing an anatomical and functional deaffer-
entation of cortical from subcortical struc-
tures. Primitive reflexes are known to occur in a wide variety of dementias, including
Alzheimer's disease² and vascular dementia.³

It is likely that the presence of undetected cerebrovascular disease accompanying pe-
ripher al 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 whose signs rep-resented had a degree of carotid stenosis of
between 60% and 99%.⁴

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

Twenty five consecutive non-amputees on
the waiting list for femoropopliteal bypass
operation were compared with 25 postope-
tative patients who had undergone elective
hip or knee replacement and a prolonged
rehabilitation. 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-
eral ischaemia. Controls were interviewed
between 6 months and 1 year after their
operation. Both groups had no history of stroke or transient ischaemic attack.

A more detailed description of instruments
is provided elsewhere.⁵ All subjects were

---

**Table 1**

<table>
<thead>
<tr>
<th>1st Episode</th>
<th>2nd Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peroneal</strong></td>
<td><strong>Tibial</strong></td>
</tr>
<tr>
<td>MCV (ms)</td>
<td>26</td>
</tr>
<tr>
<td>DL (ms)</td>
<td>7.3</td>
</tr>
<tr>
<td>F wave latency (ms)</td>
<td>7.5</td>
</tr>
<tr>
<td>CMAP (µV)</td>
<td>3</td>
</tr>
<tr>
<td>SCV (ms)</td>
<td>38</td>
</tr>
<tr>
<td>AMP (µV)</td>
<td>16.2</td>
</tr>
</tbody>
</table>

MCV=motor conduction velocity; DL=distal latency; CMAP=compound motor action potential; SCV=sensory conduction velocity; AMP=amplitude; L=left; R=right.
examined using a rating scale for the examination of frontal release signs (FRSS),
with nine operationally defined items, each on a seven point semiquantitative scale. The
nine reflexes were paratonia and palmonental, hand grasp, foot grasp, glabellar, rooting,
spontaneous and visual/tactile sucking reflexes. Neupropsychological 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.

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

Patients with peripheral vascular disease had a higher mean score on the frontal release signs score than controls (5.8 (SD 4.6) vs 1.7 (SD 1.0)).
Mann-Whitney U = 300, Z = −3.33, two tailed p = 0.001, as well as on
glabellar and rooting reflexes (table). Only one variable (trailmaking B test time) was
entered into the equation; this accounted for
23% of the variance in FRSS score (B = 4.6,
95% confidence interval (95% CI) (B = 1.3–8.0, p = 0.01).

In peripheral vascular disease, there is lim-
ited information available concerning the intellective and neurological sequelae of
coeexisting 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 differ-
ences between the groups in verbal fluency,
concentration, abstract thought, perception, and constructional skills.1 Another study by the same group found poorer performance in psychomotor
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.1,2

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

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

RAHUL RAO
Department of Old Age Psychiatry, Maudsley Hospital
Institute of Psychiatry, London
Correspondence to: Dr Rahul Rao, Department of
Old Age Psychiatry, Guy's, King's, and St Thomas
Medical School, Job Ward, Thomas Guy House,
Guy's Hospital, St Thomas Street, London SE1
9RT, UK. Email rahoo@globenet.co.uk

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

<table>
<thead>
<tr>
<th>Hand grasp</th>
<th>Foot grasp</th>
<th>Glabellar</th>
<th>Palmonental</th>
<th>Paratonia</th>
<th>Rooting</th>
<th>Snout</th>
<th>Sucking (tactile)</th>
<th>Sucking (visual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>pValue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>274.0</td>
<td>0.15</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>
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<tr>
<td>1.0</td>
<td>0.001*</td>
<td></td>
<td></td>
<td>0.15</td>
<td>0.29</td>
<td>0.01*</td>
<td>0.44</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*Higher mean score in people with peripheral vascular disease.
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 reversals (for example, “aminex”, “executive”). The formal testing identified no consistent evidence of visuospatial deficits or constructional apraxia. The findings were interpreted as inconsistent with the patient’s history but the possibility of a factitious aetiologies 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 neurologiological diagnosis of malingered or factitious disorder.

No further investigations were performed and the patient was transferred via the original hospital to a rehabilitation facility and subsequently discharged to home. Confronted with the findings of the video monitoring the patient appeared sanguine and accepting of the evidence that he should be able to move his left side. Six months later he was ambulatory but otherwise not significantly improved. He had been assessed by a psychiatrist but had refused psychiatric follow up, electing instead to be followed up by a psychologist. He understood his diagnosis 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 symmetrical 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.1 In retrospect, the severe neglect on clock drawing was perhaps “too good to be true”, especially in the light of the near normal line bisection demonstrated on the same day. The mirror image distortion of the house was also very unusual and, furthermore, the mirror reversal itself is evidence of lack of clinical neglect. The distortion of the cube, however, could easily be misinterpreted as evidence of organic constructional impairment if seen in the absence of the other relevant clinical and laboratory information.

During follow up, the patient admitted to feeling tremendous occupation related stresses, and described how he had come to both fear and detest his job. Given the clear benefit to the patient of removal from his work environment, the relapse of his symptomatology just as he was scheduled for return to work after his first non-organic hemiplegic episode, and the intentional reasons required to feign poor clock drawing and constructional apraxia, there is much to support a diagnosis of malingering.1 Nevertheless, classification as a factitious disorder is at least as justifiable in view of the patient’s willingness to undergo medical investigations, including video monitoring.

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


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 reaction was present on the left. In addition, visual extinction and neglect were present.

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

Four weeks after the stroke he first acknowledged that his left arm belonged to him, but he was acutely concerned about dealing with it. By this time he had a moderate hemiplegia and recognised “a little weakness,” but continued to insist that he was well and able to return to work. By the 6th week another patient more consistently acknowledged that he was weak on the left side of his body. A request for disabled housing “so that I won’t be a burden to my family” seemed to indicate an appreciation of his impairment. The patient was found to be florid 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 following the stroke before being 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 treated. His girlfriend was surprised when he kissed her in front of the staff. He spontaneously recalled believing that the left arm “smelled funny” was another reason he wanted the nurses to take it away.

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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 lost. 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.

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

Witnesses reported that the patient would, while walking, suddenly collapse to the ground where he would remain unresponsive, inaccessible, and motionless for 9 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. Observation of the episode for four hours 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 of epileptic in origin and therefore before he was started on phenytoin, with no benefit. Carbamazepine was added, again with minimal effect.

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

Cardiovascular and neurological examination was normal as were MRI and routine interictal EEG. Sixteen channel ambulatory EEG using an Oxford Instruments digital EEG receiver was performed continuously for 340 hours before an episode was captured. Internally, rare spikes were seen over the right frontocentrotemporal region during sleep. The onset of the episode was not witnessed and the patient was found lying on the floor, regaining consciousness at about 07:06. The event EEG showed a short run of bilateral semirhythmic 2–3 Hz activity at 07:04:34 (figure A), persisting for 8 seconds before being obscured by muscle and movement artefact. Twenty four seconds later a second EEG change, at 07:04:58, the ECG changed from sinus rhythm at 90 bpm to a brief period of sinus bradycardia, followed by a period of asystole with only very occasional ventricular complexes present for 10 seconds (figure B). After a few seconds of bradycardia there was a tachycardia, sinus rhythm was restored. Throughout the episode the QT interval on the ECG remained within normal limits. The ECG became visible again 16 seconds into the asystolic period, at which time it was dominated by diffuse low amplitude slow activity at <1–2 Hz which persisted for 10 seconds (figure C). This was followed by marked attenuation of the EEG activity over the next 10 seconds before large amplitude generalised rhythmic <1Hz activity became apparent. Diffuse theta activity was seen for a further 15 seconds before the ECG returned to its resting state.

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

Cardiac dysrhythmias are an uncommon but serious consequence of partial seizures. Our case is unusual because of the duration of asystole. In a series of 26 patients with 74 temporal lobe seizures in which simultaneous EEG and ECG recordings were acquired, ictal arrhythmias occurred in 52% of seizures, the commonest being irregular abrupt changes in heart rate, (both acceleration and deceleration) occurring towards the end of the period of EEG abnormality.1 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.2,3

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 activity 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.4 Additionally, prolonged stimulation resulted in ventricular ectopics, heart block, QT prolongation, and death. In presurgical temporal lobectomy patients stimulation of the left insular cortex (particularly posteriorly) produced bradycardia and a depressor response significantly more often than tachycardia and a pressor effect.5 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 the recording. 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 R JUGG-GU NN JOHN S DUNCAN SHELDON 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

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

Hereditary neuropathy with liability to pressure palsy (HNPP) typically presents recurrent pressure palsies of peripheral nerves, such as the axillary, median, radial, ulnar, or peroneal nerves, at common entrapment sites. Respiratory muscle weakness has not been previously reported in HNPP. We describe a patient with HNPP with respiratory failure and proximal muscle weakness who was not a smoker and had no other known medical problems.

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 the Horton Red Cross Hospital with respiratory failure and 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 disease or other medical problems. There was no family history of neurological disorder, including entrapment neuropathies. After a few months, he noted 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 incapacitated 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 hypoactive in all limbs. The patient’s sensations of touch and pain were mildly impaired in the four limbs. Sensation was normal. His vital capacity was 1.9 l (55% of the normal mean) in the sitting position, but 1.3 l (38%) in the supine position. The percentage of forced expiratory volume in 1 second was normal (99%) (graph 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)) nerves, and moderate decreased conduction velocities in the right ulnar (54 m/s (normal>65)) and median nerves (normal>45), ulnar (45 m/s (normal>49)), tibial (35 m/s (normal>38)), and peroneal (29 m/s (normal>41)) nerves. There were moderate decreases in the amplitude of compound action potentials in all the nerves tested, and an amplitude reduction of 50% was detected across the cubital tunnel of the right ulnar nerve. Minimum F wave latencies were prolonged in all the nerves tested. The latency in the right phrenic nerve was slightly
of myelinated fibres was reduced (5726/mm² normally thin axonal myelin sheaths. The density of the myelin sheath and some abnormalities were scattered tomaculous thickening of the myelin sheath and some abnormally thin axonal myelin sheaths. The density of myelinated fibres was reduced (5726/mm²). A gene analysis disclosed a 53% gene dose of PMP-22 related to normal controls, using Southern blots of DNA digested with EcoRI. Given the possibility of superimposing demyelinating neuropathy, especially chronic inflammatory demyelinating polyneuropathy, oral prednisolone (60 mg/day) was given for 1 month. However, the patient’s clinical condition did not respond to this treatment. Pulmonary dysfunction and proximal muscle weakness were almost steady during the next 3 years.

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

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

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

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

We thank Dr T Yamamoto from the University of Occupational and Environmental Health for the gene analysis and Mr T Nagase from Chiba University for his technical help with the sural nerve biopsy.
venous thrombosis is often asymptomatic, or presents with non-specific pain, it is probably unrecognised in many cases.1 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. Electrodiagnostic studies were consistent with partial right accessory nerve neuropathy with minor denervation of the right trapezius. Cervical ultrasonography and MRI demonstrated right internal jugular venous thrombosis. The patient was treated with a shoulder support, analgesics, and low dose aspirin. There was no significant clinical change 1 year after CEA. Repeat electrodiagnostic studies were consistent with chronic right spinal accessory neuropathy, and repeat ultrasonography showed persistent right internal jugular venous thrombosis. Spinal accessory nerve neuropathy was first reported as a complication of CEA in 1982.6 Since then, there have been several case reports and small series.7 A 1996 review of reports of cranial neuropathy after CEA disclosed only one patient with spinal accessory neuropathy in over 3000 cases.8 Although the authors did not include several other reports9 which, taken together, may seem to suggest a somewhat higher incidence, the overall small number of reported cases in proportion to the hundreds of thousands of CEA’s that have been done worldwide suggests that clinically significant spinal accessory neuropathy is a rare complication. Moreover, spinal accessory nerve neuropathy after CEA may be more frequent. The cause of spinal accessory neuropathy after CEA is usually not well established, but intraoperative nerve stretching or compression from retraction is most often invoked.10 Delayed onset (after 3 weeks) has been noted in some; for these patients, postoperative inflammation and scarring seem more likely causes. Spinal accessory nerve transection or ischemia/infarction (arterial or venous) are other possibilities. As in our patient, high carotid dissection and retraction have been reported to precede spinal accessory neuropathy.11,12

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

From our search, internal jugular venous thrombosis after CEA has been reported in only one case.2 As Southcott et al noted, retraction of the internal jugular during CEA may cause the skin and subcutaneous structures to retract and extend into the musculature, leading to thrombosis from venous stasis or endothelial injury. Other causes of internal jugular venous thrombosis include jugular canulation, blunt cervical trauma, and a hypercoagulable state. Internal jugular venous thrombosis may occur as a complication after neck dissection, often with recanalisation after several months.3

The presence of induration about the incision site and a palpable supraclavicular cord in our patient led us to suspect venous thrombosis. Although the authors did not include several other possibilities. As in our patient, high incision and retraction resulting from a high carotid bifurcation would place the nerve at risk. Whether this realisation may lead to any technical modification to decrease the risk of spinal accessory neuropathy in those with a high bifurcation is unclear.

Although the onset of either spinal accessory nerve neuropathy or internal jugular venous thrombosis in our patient cannot be determined precisely, it is likely that both developed at about the same time. The delayed worsening of spinal 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 nerve neuropathy after CEA, implies considerable axonal injury, but does not clarify the manner of injury.

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

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

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

A 33 year old man had a severe apasia 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. Cerebral ultrasound duplex scanning and cerebral angiography were normal. Cerebral CSF examination and EEG were also normal except for a patent foramen ovale.

The patient had no vascular risk factors, in particular no tobacco use, and he was perfectly fit until his stroke. He was a sportsman, with 2 hours daily intensive training for body building. He was working as a baggage handler in an international airline company. During a recent journey to Miami, Florida, he bought tablets of “energy pills” in a shopping store to enhance his athletic performances. The first drug contained MaHuang extract (corresponding to 20 mg ephedra alkaloids), 200 mg coffeeine, 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 excluded as he recently took a transatlantic flight, there was no deep venous thrombosis and D-dimers were normal. However, ephedrine has an indirect sympathomimetic action by increasing plasma norepinephrine levels, especially in asthmatic patients, for arteriole vasconstriction in addition to other catecholaminergic effects. Both ischaemic and haemorrhagic stroke associated with ephedrine use have been reported.1 Acute myocardial infarction and acute psychosis have also been reported after taking ephedrine and other sympathomimetic drugs.2 Ephedrine and its metabolites are natural products that are used in non-prescription medicines for multiple uses, ranging from ointments and oral preparations to herbal and sports nutraceuticals that are used in non-prescription tablets in some countries.

Although no cardiovascular side effects have been reported with the use of creatine monohydrate, this compound, used in association with other drugs as energy supplement may have deleterious side effects. This may be particularly true when used at high doses in combination with sympathomimetic drugs as in our patient. Renal dysfunction has also been reported after oral creatine supplements. Our patient had a slight increase in creatine serum concentration; although

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

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 dysesthesia of the upper quadrant of her face for 1 year. In addition she had intermittent ipsilateral headache. A left sided facial palsy and hypoguesia 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 hypoguesia of the left half of the tongue. Speech was slightly dysarthric. During examination dystonic and choreic movements of the left facial muscles were seen. The dystonic grimacing increased when the patient was being observed. There were also intermittent jerky dystonic head movements with turning of the head to the left, associated with slight elevation of the left shoulder. The facial movement disorder was clearly different from hemifacial spasm. There were no tonic or clonic synchronous contractions of facial muscles and no signs of involuntary coactivation. The patient barely noted the dyskinesias. Audiometry showed a hearing threshold at 30 Db on the left side and lack of stapedius reflex on the left side. Oculovestibular response to caloric stimulation was...
decreased on the left side. Furthermore, there was mild left dysarthrochokinesia.

Neuropathy 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 cava Meckel with marked displacement of the brainstem to the contralateral side (figure A and B). Angiography showed a discrete blush of the tumour as typically seen in meninges. The tumour was totally removed by a combined transpetoral supratentorial and infratentorial presigmoid approach. The postoperative course was uneventful and there were no new deficits. The facial palsy improved slightly as well as the trigeminal hypoaesthesia. Audiometry remained unchanged. Postoperative imaging showed no residual tumour and the displacement of the brainstem 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 hypokinetic movement disorders. Such a relation is supported also by the absence of a family history of movement disorders and the absence of previous exposure to neuroleptic medication. Hypokinetic movement disorders due to tumours of the brainstem or of the posterior fossa have been reported only rarely. Asymmetric blepharospasm was recently found in a patient with an ipsilateral mesencephalic cyst.1 Hemifacial spasm was seen in pontocerebellar neoplasms, meningiomas, and epidermoid tumours of the cerebellopontine angle.1 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 suggested previously.1 Alternatively, enhanced excitability of brainstem interneurons has been suggested. This pathophysiological mechanism is supported by the findings of blink reflex studies in patients with blepharospasm, spasmodic dysphonia, and cervical dystonia. Tolosa et al found significantly less inhibition of the test stimulus polysynaptic late response and marked enhancement of the recovery curve of the late response under such conditions compared with the response in healthy subjects. The late response under such conditions comprises an enhancement of the recovery curve of stimulus polysynaptic late response and may indicate a supersensitivity of brainstem interneurons.1 Although this mechanism is supported by blink reflex studies in focal dystonias, enhanced excitability of brainstem interneurons in cranial dystonia and spasmodic torticollis has not been shown.


Acute multifocal cerebral white matter lesions during transfer factor therapy

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

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

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

Laboratory examination on admission showed a slight increase in total serum protein (8.4 g/l, normal 6.0–8.0 g/l, although the serum protein fraction was normal), antistreptolysin tites (355 UI/ml, normal <200 UI/ml), and anticardiolipin IgG (30 UI/ml, normal 8–12 UI/ml). Negative results were obtained for Adenovirus, Enterovirus or Borrelia burgdorferi. Venereal disease research laboratory test, erythrocyte sedimentation rate, fibrinogenemia, C reactive protein, rheumatoid factor, Waaler-Rose, protein electrophoresis, antinuclear antibody-anti-DNA, antimitochondrial, anti-ENA, anti-smooth muscle, and antineutrophil cytoplasmic antibody. Two MR scans at 1 and 4 months after onset showed slightly increased deep tendon reflexes on the right side and was normal 40 days later; all laboratory analyses were normal except for antistreptolysin tites (265 UI/ml). Two MR scans at 1 and 4 months after onset showed progressive reduction of lesions without contrast enhancement but a new large lesion in the left occipital white matter, which showed moderate contrast enhancement. At present, after 5 years, the patient is in a good state of health and neurological examination and laboratory tests are normal.

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

THOMAS POHLE
Department of Neurosurgery, Inselspital, University of Berna, Berna, Switzerland

JEAN-MARC BURGUNDER
Department of Neurology

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 extending to the centrum semiovale exhibiting thick annular enhancement.
the diagnosis of vasculitis or neuro-Behçet's disease although in the absence of biopsy. In fact, the clinical, laboratory, and MRI findings were not typical and a low titre of anticitrullinated antibodies is found in 2% of healthy subjects.1

The occurrence at different time of focal cerebral white matter lesions highly supports the diagnosis of multiple sclerosis, but some clinical and laboratory findings in the our patient are not typical for this condition. Mental confusion is not common at the onset of multiple sclerosis whereas it is often found in acute disseminated encephalitis.1 In addition, CSF without oligoclonal banding argues against a diagnosis of multiple sclerosis, whereas it is commonly found in acute disseminated encephalitis.1 On the other hand the possibility that acute disseminated encephalitis may recur has been accepted1 and on the basis of the patient's clinical picture and CSF, we favoured such a diagnosis.

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

Although the hypothesis that dialysable leucocyte extract had triggered an autoimmune disorder in our patient cannot be proved, our finding is in line with the report of multiple cerebral lesions after therapy with IL-2 in patients with malignancies or HIV infections.2 On the other hand, the fact that acute disseminated encephalitis is often correlated with the administration of foreign proteins, such as during vaccinations or viral infections3 led us to postulate in this patient a stimulating or potentially activating sub-stance so it is impossible to pinpoint which one could have been responsible for the demyelinating effect seen in our patient. This notwithstanding, our finding indicates that neurological surveillance is worthy in patients assuming dialysable leucocyte extract therapy.

Correspondence to: Dr Francesco Giuseppe Foschi, Semesiatica Medica, Dipartimento di Medicina Interna, Epatologia e Cardioangiologia, Università degli Studi di Bologna, Policlinico Sant'Orsola, via G Massarenti 9, 40138 Bologna, Italy. Telephone 0039 51 308943; fax 0039 51 308966; email: fgfoschi@tin.it

Brain CT, axial section: dense calcific deposits in the basal ganglia, thalamus, and orbitofrontal cortex consistent with Fahr's disease.


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 calciifications.

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 impairment of fine finger movements, dysgraphaesthesia on sensory testing, and a maneristic gripping handshake. There were no extrapyramidal...
symptoms. His IQ score was in the low range (WAIS-C=85 at the age of 13; Barbeau-Pinard=82 at the age of 17). He also presented an impairment on the Tower of London test, which measures executive function, and in a task assessing the understanding of others’ intentions. These two findings are reliably present in pervasive developmental disorders, in this IQ range. In addition, his performance on the Tower of Toronto test disclosed impaired performance in procedural learning. Psychiatric assessment showed scores above the cut off for autism according to the autism diagnostic interview (ADI), a standardised interview that requires specific training and those administering it to have a 0.90 reliability with other researchers. The subject was positive for the diagnosis of autism, being above cut off values in the three relevant areas of communication, social interactions, restricted interests, and repetitive 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). SPECTCT showed increased activity in basal ganglia relative to the cerebral cortex. A fine-needle biopsy of the parathyroid glands showed an absence (normal 1.0–6.55 µM/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 and autism is scarce and inconclusive. Although the tempo-orbital region is the most often involved in pervasive developmental disorders and autism, is suspected from reported findings of executive function deficits and from occasional findings of fronto-hypotemplate 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 calcium deposits in the basal ganglia, thalamus, cerebellum, and orbitofrontal cortex, 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 hyperparathyroidism, 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 fronto-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, similar to some others suggests that dysfunction in key brain circuits may result in behavioural and cognitive abnormalities curiously 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 a typical cause of compression of the upper spinal cord. The craniovertebral junction must be considered within the differential aetiologies. Cognitive and behavioural abnormalities currently indistinguishable from autism 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 fronto-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. 

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

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

Brain CT on admission showed a discrete and linear high density at the left ambient cistern. 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 haematomata 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 cranio-cervical injury. Responsible lesions for sensory impairment, detectable by neuroimaging studies, almost always accompany associated neurological deficits. To our knowledge, a selective injury at the spinothalamic or trigeminothalamic tracts due to closed head injury has not been highlighted in the neurological literature.

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

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

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

Toluene induced postural tremor

We read with interest the article by Miyagi et al1 and comment on the medical treatment of toluene induced tremor. Microdialysis experiments in rats have shown that inhalation of toluene increases extracellular γ-amino butyric acid (GABA) concentrations within the cerebellar cortex2 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.3 Denervation of certain cerebellar pathways is probably responsible for the loss of this dopaminergic innervation.4 Dopamine agonists could therefore be of potential interest in the treatment of toluene induced tremor. This hypothesis was explored in a recently described case,5 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 cerebellar atrophy and marked low signal intensity in globus pallidi, thalami, red nuclei, and substantia nigrae on T2 weighted MRI. As our patient's tremor was progressive, medical treatment with a dopamine agonist was considered. One particular agent (amantadine) caught our attention because it had proved successful in the treatment of postural tremor in a case of heredodegenerative disorders in which the dentatorubro-olivary system is affected. In addition, there is evidence that catecholaminergic pathways are also involved in this type of ataxias, supported by loss of expression of several neurotransmitters in the CSF of patients with heredodegenerative ataxias.6 In our patient, amantadine hydrochloride (100 mg twice daily) abolished postural tremor and ataxia completely over a 3 month period. Subsequently, the treatment was discontinued, which resulted in relapse of the tremor and ataxia. He was rechallenged to amantadine hydrochloride (100 mg twice daily) and ataxia and postural tremor were abolished. In addition, the patient reported a subjective alleviation in the frequency and severity of his memory impairment.

We think that there are two problems with this study that should make the physician cautious about applying the factors identified by Nabbout et al 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 ataxocytotasia and risk factors, and hence the positive predictive value of any screening test in a general population of patients with tuberous sclerosis complex is not well understood.

We therefore consider that the natural history of these lesions in the general population of patients with tuberous sclerosis complex needs to be studied, and hence the positive predictive value of any screening test in a general population needs to be determined. In addition, MRI may not be the best means of identifying SEGAs. Finally, the authors have made a potentially misleading decision to exclude more than half their study sample because they do not have lesions close to the foramen of Monro. It is not certain that all SEGAs arise from lesions close to the foramen. They may arise in the fourth ventricle. Furthermore, the large number of lesions in the lateral ventricles has, in the past, precluded accurate determination of their point of origin. The study selects 24 of 60 patients who had met their entry criteria but does not state how many of the excluded 36 patients had no subependymal nodules or nodules that were not “near the foramen of Monro”. Indeed no definition is given for what constitutes proximity to the foramen. The authors were apparently not blinded at the point when they selected which patients had lesions near to the foramen and therefore there is an obvious issue of potential selection bias. The consequence of excluding these patients may have been that false significance is given to their results. The data they present are fragile. Consider, for example, the consequence of introducing from these 36 non-selected patients a hypothetical single case that had a family history of tuberous sclerosis complex and a subependymal nodule which enabled with gadolinium. The effect would be to remove the stated statistical significance (using Fisher's exact tests) between the outcome and both of these explanatory variables.

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

FINBAR J K O'CALLAGHAN ANDREW LUX

Correspondence to: Finbar J K O'Callaghan, Bath Unit for Research in Paediatrics, Royal United Hospital, Bath BA1 3NG, United Kingdom


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

Over the past few years, we have noticed a growing interest in the renaming of this clinical form of ALS, which has its origins and predomination in the proximal muscles and the upper limbs and little or no effect of either a bulbar nature or in the lower limbs. Thus Hu et al coined the term fatal arm syndrome, to describe a subgroup of patients affected by ALS that predominantly showed signs of lower motor neuron disease in the upper limbs, without significant functional involvement of other regions on clinical presentation. This subgroup of patients was clinically characterised by the display of progressive atrophy and weakness affecting the proximal muscles in the upper limb muscles in a more or less symmetric manner.

Recently, along these lines, Kata et al described a series of patients affected by ALS, which is predominantly shown signs of lower motor neuron disease restricted to the upper limbs, with severe proximal and varying degrees of distal involvement, calling it amiotrophic brachial diplegia syndrome. Other terms used in the past to refer to this form of ALS have been danging arm syndrome, suspended form, orangered sign, dead arm sign, bibrachial palsy, rizomelic amyotrophy, and the idea of naming it a distinctive phenotype of a neurogenic
"man-in-the-barrel" syndrome has even been suggested. Probably all these terms used to define this variation of ALS are synonyms for an older, well-known condition, the scapulopha- langer form, or the chronic anterior poliomyelitis reported by Volkmann in 1886 and known in Franco-German literature as Vulpen-Bernhardt’s form of ALS. At certain stages of the disease’s clinical course, it is probably difficult to differentiate it from progressive muscular atrophy (PMA). Some authors have said that PMA with late onset scapulopha- langer distribution (over 45 years of age) generally leads to ALS as a matter of course. Be that as it may, the truth is that this atypical form of amyotrophic lateral sclerosis behaves differently from typical ALS. The comparative study with the rest of the ALS group supplied important clinical findings, such as little or no functional impairment of the bulbar muscles or legs. Hu et al also made four important statistical discoveries.

1. The prevalence of this form of ALS constituted 10% of the ALS group as a whole (p = 0.051). The age of onset of this form was similar to the rest of ALS. (3) There was a clear predominance among men (the male/ female ratio was 9:1 in this form, compared with 1.5:1 in the total ALS group). (4) There was a longer median survival (a median survival of 75 months compared with 39 months in the ALS group).

Some of these patients have a long ALS clinical course, in that they usually preserve ambulatory ability, albeit with gait disorders, for more than 5 years after the onset of symptoms. On a personal level, we also note two findings characteristic of these patients. In the initial stages of the illness, there is no effect on the diaphragm and the respiratory muscle failure occurs much later than in the typical form of ALS. This can be seen in the follow up of the results obtained in the respiratory function tests (FVC, PIMax, and PEmax).

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

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

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


Sasaki replies:

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

Over many years, several researchers have recognised this peculiar distribution of muscular atrophy in clinical practice. The clinical manifestations consist of the muscular atrophy confined to the 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, and it is of interest that many terms have been coined to describe this peculiar pattern of the muscular atrophy such as dangling arm, orangutan sign, dead arm syndrome, and amyotrophic bulbar diplegia syndrome. Some researchers classified into a category of motor neuron disease (ALS or spinal progressive muscular atrophy). However, others could not exclude the possible cause of cervical diseases such as associated motor loss in the upper extremity. In fact, these patients had cervical abnormalities such as cervical hypotrophy and ossification of posterior longitudinal ligament disclosed by cervical radiography, MRI, or myelography. By contrast with clinical awareness of this peculiar pattern of muscular atrophy, no pathological correlation of cervical hypotrophy has been made until we first reported necropsy cases in our articles. Now, these patients with their peculiar pattern of muscular atrophy are considered to be ALS or a subtype of ALS. In my private opinion, “dangling arm syndrome” or “dead arm sign” seems to be the most suitable term depicting this type of motor neuron disease.

I agree with Hu et al reporting four important statistical discoveries in this form of ALS: the prevalence percentage of 10% of the whole ALS group, the similar age onset to the rest of ALS, a predominance among men (the male/female ratio was 9:1 in this study), and a longer median survival. It is clinically important to give wider publicity to the existence of this atypical form of ALS to avoid unnecessary surgical intervention for cervical abnormalities.

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

Correspondence to: Correspondence to: Dr Josep Gamez, Servicio de Neurología, Hospital General Universitari Vall d’Hebron, Passeig Vall d’Hebron 119–135, 08035 Barcelona, Spain. email: 12784jgc@ccib.es

isolated dysarthria

We read with interest the article by Urban et al. Using transcranial magnetic stimulation, the authors demonstrated electrophysiologically evidence for a central monoparesis of the tongue in patients with isolated dysarthria from stroke. As in their patients transcranial magnetic stimulation induced absent or delayed corticoluminal responses at the tongue, the authors ascribed isolated dysarthria to interruption of the corticoluminal pathways. On the whole, the authors have made a fundamental examination, but we would like to comment on the underlying mechanism of isolated dysarthria.

As in the case of isolated dysarthria reported by Urban et al, all of our patients with isolated dysarthria had lacunar infarctions involving the internal capsule and corona radiata. Measurement of cerebral blood flow with IMP-SPECT in these patients disclosed frontal cervical hypoperfusion, particularly in the anterior opercular and medial frontal regions. Anterior opercular lesions produce facio-pharyngo-glosso-masticatory paresis (anterior opercular syndromes), and damage to the medial frontal regions, including the supplementary motor area, causes speech expression disorders. White matter lesions can disrupt afferent and efferent fibre connections in sensorimotor and corticocortical fibres as well as the corticobulbar fibres. In fact, lacunar infarctions around the internal capsule-corona radiata are likely to underlie these ascending and descending pathways.

To assess corticopontocerebellar tract function, Urban et al investigated cerebellar blood flow in patients with isolated dysarthria using HMPAO-SPECT. They demonstrated that isolated dysarthria 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. Linguo-palatal paresis 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 production as well as a lingual monoparesis. Although interruption of the corticolinguinal pathways is a likely cause of isolated dysarthria, it should be borne in mind that damage to other descending and ascending projections may contribute to isolated dysarthria.


Urban et al reply:

Ogawa 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 a single lesion collected by us is more appropriate to correlate lesion topography with impaired function. The findings of Oguda et al are in line with our conclusion that interruption of the corticocortical pathway is a key factor in the pathogenesis of chorea of extracerebellar origin. Obviously, impairment of the corticocortical tract of one hemisphere by a single small lesion is an adequate condition for dysarthria. The patients of Oguda 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 hyperperfusion as disclosed by SPECT in the series of Oguda 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 HOFF

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

The mean disease duration of our nine patients with Huntington’s disease was 6.2 (4.1) years which is actually shorter than the duration of the six patients reported by Hanajima et al (8.3 (5.9) years). Most of our patients could be considered in an early stage of the disease, as 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. Chorea itself is often reduced in the more advanced Huntington’s disease stages. It is unlikely, therefore, that any neuropsychological approach can test purely chorea even in the early Huntington’s disease stages. In addition, different mechanisms are involved in Huntington’s disease and other choreas as suggested by the lack of impairment of somatosensory evoked responses and long latency stretch reflexes in the second.

We were not really surprised at the results of Hanajima et al as we do share their opinion that patients with Huntington’s disease may be characterised by large individual differences in the involvement of motor cortical areas. Actually, three patients in our study showed an amount of intracortical inhibition within the confidence limits of the control population. We also think that the impairment of intracortical inhibition is likely to develop during the progression as we did not find any change in four patients, two of them already reported, with positive DNA testing but completely asymptomatic. The discrepancies between the two studies are more likely to be explained, at least in part, by some methodological differences. For instance, the amplitude of the control response was larger in our set (approximately 1.2 mV compared to 0.7 mV in the study of Hanajima et al). This may induce a different sensitivity of the test, and the amount of intracortical inhibition in our normal controls is greater (see also1) than in the study of Hanajima et al.

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

C TROMPETTO

Department of Neurological Sciences and Vision, Movement Disorders Clinic, University of Genoa, Via De Toni S, 1, 16132 Genoa, Italy


The authors reply:

We are 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 our two groups of patients. Although the duration of the disease is one factor to judge the disease stage, the severity of the disease (stage of the disease) is also positively correlated with CAG repeat number.

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

We also consider that methodological differences are very important in paired magnetic stimulation. The results strongly depend on the intensities of both a conditioning and a test stimulus. Especially, the intensity of the conditioning stimulus is critical. We have no difficulty in showing normal inhibition, but have much difficulty in showing reduced or absent inhibition because of such marked dependence of the results on the intensities of stimuli. Therefore, we used the intensity 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 in our study of chorea.4 We did not need to change the intensity of the conditioning stimulus because we always obtained a normal inhibition with this intensity. We consider that this is very important. If using a suprathreshold (active threshold) conditioning stimulus, a facilitatory effect must often supersimpose on the intracortical inhibition. This makes the interpretation difficult. Was the intensity of 80% of the resting threshold the active threshold in their patients? In our experience, 80% of the resting threshold was sometimes above the active threshold. These factors must be considered in interpreting the results of paired magnetic stimulation.

Such a methodological problem is inherent in human studies because we have no direct way of detecting the threshold of the motor cortex. Our two results must be true. We may have two completely different interpretations of these results. (1) The intracortical inhibition is normal in Huntington’s disease. Abbruzzese et al showed the reduced inhibition because they used a high intensity conditioning stimulus with which the degree of the
intracortical inhibition is often decreased even in normal subjects. The 80% of the threshold for relaxed muscles must correspond to different values relative to the threshold for active muscles in patients from that in normal subjects. (2) The intracortical inhibition is decreased in the patients with Huntington's disease. This slight abnormality could be detected with their method but not with ours because their method has better sensitivity in detecting an abnormality than ours. Whichever is true, the intracortical inhibition must be normal or slightly disturbed in Huntington's disease.

R HANAJIMA
Y UGAWA
Department of Neurology, Division of Neuroscience,
Chiba University School of Medicine, Chiba, Japan


Critical closing pressure: a valid concept?

Czosnyka et al. 


3 Burton AC. On the physical equilibrium of the cerebral artery during strong hypocapnea. In our paper we confirmed empirically that both CCP1 and CCP2 produced the same values in a group of patients after head injury, therefore the mathematical consideration of Diehl (equations 1-5) must contain an error!

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

Definition of CVR0 as FV/(ABP-CCP) is completely artificial and lacks a physiological basis. It is rather taken from the geometrical interpretation of figure 1 in. In our material equivalent of parameter CVR0 (as defined by Diehl) is 1.007 (SD 0.31) and CVR1 0.972 (SD 0.29), the difference is 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 CVR 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 be noted that this is 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 under constant pressure reactive or ICP was not always constant.

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

Reduction in the neuronal activity of the subthalamic nucleus leading to diminished excitation of the globus pallidum internum is associated with chorea-ballism in monkeys. Levodopa induced dyskinesias are currently thought to share a similar pathophysiology but recent findings also suggest that abnormalities in neural firing in the globus pallidum internum may be relevant. Data from both parkinsonian monkeys and patients with Parkinson’s disease submitted to lesion or functional blockade of the subthalamic nucleus are in keeping with such a general principle, but the threshold to induce dyskinesias in the parkinsonian state is higher than in intact animals. The case recently described by Figueiras-Mendez et al. is extremely interesting as it suggests that functional inhibition of the subthalamic nucleus by high frequency stimulation blocks levodopa induced dyskinesias. This is at odds with the current pathophysiological model of the basal ganglia. Thus, the finding of Figueiras-Mendez et al. rises the intriguing possibility that dyskinesias depend or are mediated by neuronal firing in a given region of the subthalamic nucleus, which was blocked by high frequency stimulation. Measurement ofafferent synaptic activity by the technique of 2-deoxyglucose (2-DG) uptake showed an increment in the subthalamic nucleus compatible with increased inhibition from the globus pallidum externum, particularly in the ventromedial tip of the nucleus. This contrasts with the findings in monkeys with chorea induced by pharmacological blockade of the globus pallidum externum, in which 2-DG uptake was maximal in the dorsolateral portion of the subthalamic nucleus, where the sensorimotor region lies. A recent anatomical study also showed that the cortical-subthalamic pathway conduction is somatotopically segregated, so that fibres from the supplementary motor area project to the most medial portion and fibres from the primary and premotor areas terminate in the lateral region of the subthalamic nucleus. All this heterogeneity may have pathophysiological relevance, describing 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 or reject the role of the subthalamic nucleus in the origin of levodopa induced dyskinesias, there is a crucial issue to resolve—namely, the location of the tip of the stimulation electrodes.

There are several points leading us to question the actual site of action of the electrode: (1) Stimulation of the subthalamic nucleus in Parkinson’s disease has been associated with the production of dyskinesias only related to levodopa intake. Moreover, Benabid et al who pioneered this technique, consider the induction of dyskinesias by high frequency stimulation of the subthalamic nucleus as a good indicator of a very positive response. The finding of Figueiras-Mendez et al. would seem to nullify 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 recording electrodes are placed ventrolaterally to the thalamus in sagittal planes 11 mm or less, neuronal activity is characterised by action potentials of large amplitudes (0.5–1 mV) with low background activity, tonically firing neurons, and absent sensorimotor responses (“driving”). All these characteristics seemed to be present in the patient discussed here. Neuronal activity in the sensorimotor representation of the subthalamic nucleus is different from the above but on occasions the distinction may not be easy. Accordingly, it is very important to document in more detail the findings in the case of Figueiras-Mendez et al. Ideally we would like to see the trajectory and length of the different recording tracks, the effects of microstimulation, and the post surgery MRI with measurement tracks of the tip of the electrodes. If, as assumed, the subthalamic nucleus was indeed correctly targeted in this patient, the pathophysiology of the basal ganglia will need to be revisited.

J A OBESO G LIZAZARO J GURIDI E RAMOS Centro de Neurologia y Neurocirugia Functional, Clinica Quiron, San Sebastian, Spain

J A OBESO M C RODRIGUEZ-OROZ Hospiten, Tenerife, Spain

Hospitale de Navarra, Pamplona, Spain

Correspondence to: Professor J A Obeso, 30 Cizur Artea, Cizur Mayor, 31180 Navarra, Spain.


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 subthalamic nucleus was based on the filling criteria: (a) high frequency discharge (25 Hz or higher) within the nucleus; (b) a tonic (regular), phasic (irregular) or a rhythmic pattern of discharge; (c) response to voluntary/passive movements. When rhythmic discharges were recorded irregular passive manipulations were performed or the patients asked to move the limbs irregularly; (d) response to tremor arrest. Positive cells were considered based on their firing pattern with the EMG and the accelerometer recorded simultaneously. Artificial manual stopping 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 above the subthalamic nucleus; (f) the subthalamic nucleus and zona incerta with proper characteristics; (g) a change in the background basal noise when entering the subthalamic nucleus. A higher activity is observed; (h) the activity of substantia nigra pars reticulata cells when lower lowering the microelectrode. 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 comments: (a) Action potentials of levodopa induced dyskinesia are easily recognised from the rest of the recording cells, and are not very common. The recordings shown in the article have amplitudes less than 0.3 mV and could not be considered large amplitude potentials. We start to record activity from 3 mm before entering the subthalamic nucleus, traverse the length of the subthalamic nucleus, and go further down several mm to encounter substantia nigra pars reticulata cells. Changes in the background activity are clearly recognised and are higher when entering the subthalamic nucleus. Enough cells are recorded along the tracks experimented to consider sampling a large amplitude potential. The
low background activity found in our recordings is only due to the better signal-to-noise ratio of the electrodes used. “Good recording electrodes” depend on many variables such as tip size, tip profile, insulation material, impedance, manufacture, etc. The signal-to-noise ratio of the cells in question has the same ratio as the subthalamic nucleus cell shown by Hutchinson et al.  

(b) In our report, cells discharged tonically, but only when the symptoms are considered. This was always tested in the surgery before cementing the electrodes, assessed by ventriculography, was found along the trajectory of the electrode. Unfortunately, this point was not mentioned in the paper. It would surely have changed the opinion of Obeso et al.  

In the foci-identified patient, a total of eight neurons were recognised as belonging to the subthalamic nucleus in the right hemisphere, with a mean frequency of 74 Hz (range 38–109 Hz). Four of them responded to passive and/or voluntary movements. One of them was considered to have a high frequency of 109 Hz (range 17–98 Hz). Five cells responded to the subthalamic nucleus in the right hemisphere, and 11.5 mm for the left hemisphere.

NITRIC OXIDE IN ACUTE ISCHEMIC STROKE

The pivotal role of nitric oxide (NO) in cerebral ischaemia has been elegantly highlighted in the recent editorial by O’Mahony and Kendall. 1 Although studies of neuroprotective agents have been largely disappointing, pharmacological manipulation of NO may represent a novel means of protecting the brain from ischaemic insult. One area not discussed in the above mentioned criteria was the neuroprotective effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or “statins” in cerebral ischaemia. Preliminary studies have shown that statins modulate brain nitric oxide synthase (NOS) activity in a neuroprotective manner. Data from a murine model of ischaemic stroke demonstrate that prophylactic statin therapy reduces infarct size by about 30%, and improves neurological outcome in normocholesterolaemic animals. 2 In this investigation, statin therapy directly up-regulated endothelial NOS in the brain without altering expression of neuronal NOS. Recent findings also suggest that statin therapy influences the activities of inducible NOS. Lovastatin has been shown to inhibit cytokine mediated upregulation of inducible NOS and production of NO in rat astrocytes and macrophages, and this inhibition may represent a new and exciting suppressor of inflammatory responses that accompany ischaemia. Most interestingly, these preliminary findings suggest that statin therapy may modify the expression and activity of NOS in a neuroprotectively beneficial manner. These and other vascular effects of statins in cerebral ischaemia are potentially of great importance in both human neuroprotection and animal models. Thus the The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study 3 will help clarify their role in human cerebrovascular disease.

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

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

Correspondence to: Dr Carl J Vaughan

The comments of Vaughan and Delanty draw attention to the act of narrating might detract from realistic illusion, so reducing the emotive intensity of what was being represented. It is a device much favoured by postmodern writers, who expose the nature of fictional constructs. The intrusive medical author never dropped out of fashion, although in these days of evidence based prejudice, authorial omniscience might be considered suspect. The authors of this volume are intrusively in a guiding conversational manner that makes this book by far the most readable of the neuroimmunological texts. The book opens with a highly accessible chapter on immune responses to the nervous system. There follows a chapter that integrates the neurobiology of multiple sclerosis with contemporary issues of aetiology, cell injury, and repair. Next, a chapter on inflammatory demyelinating disorders examines the 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 especially good, 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 Bröcher, Braak et al), and several worthy reviews of treatment strategies for Alzheimer's disease including NSAIDS (Mölter), antioxidants, and radical scavengers (Röser et al). I found the review by Reisberg et al on oncogene 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.

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

The book is essentially a collection of monographs of heterogeneous content and style and the result, perhaps not surprisingly, is that some of the component parts are better than others. However, there will clearly be of particular interest to those who treat children and their families. The chapters on infantile spams and Lennox-Gastaut syndrome are informative and provide some new but speculative insights into the pathogenesis of spams. However, it was surprising that severe myoclonic epilepsy of infancy did not merit a specific chapter in view of the unique electroclinical evolution and natural history of this syndrome. The crucial issue of the cognitive and behavioural sequelae of early and frequent seizures on the immature brain, which is probably of most concern to both clinicians and families, is succinctly addressed in two chapters—although a clear and consistent cause and effect relation remains to be established.

The chapters covering basic neurophysiology, 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 is likely that many of the monographs are interesting and informative, the overall impression is that the individual parts (the chapters) are better than the whole (the book). The lack of an index is a strange omission, perhaps reflecting a prolonged editorial atypical approach, and although this militates against it becoming a well-structured reference book, the text is an erudite addition to the mossy fibre-like sprouting of the epileptological literature.

RICHARD E APPLETON


Difficult clinical problems in psychiatry come in many forms. Diagnosis often causes difficulty, particularly in cases which demand assessment of the role of physical illness in symptom formation. Perhaps for most psychiatrists practising in community settings risk assessment comes high on their list of concerns. Unfortunately, given the psychopharmacological expertise of the editors, this book is particularly interested in treatment resistance. The first 6 chapters give excellent reviews of the management of clinically relevant topics—for example, refractory schizophrenia or the difficult panic patient. The emphasis is very much on pharmacological management.

The second half of the book is more of a mixed bag, both in terms of the areas covered and the quality of the chapters. The last chapter summarises 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 involved in training. For those reasons 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.

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

E STIP, N BLACK, J M EKOÉ and L MOTTRON

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