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 ganglia. 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 Antiepileptic drugs were withdrawn to facilitate seizure recording.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 ganglia. An interictal cerebral SPECT study was repeated at 4 weeks after postictal psychosis which showed a complete resolution of hyperperfusion signal in the right temporal lobe and basal ganglia. Anterior temporal lobectomy was performed and she became seizure free after surgery.

Patient 2 was a 44 year old man with intractable complex partial seizures since the age of 30. His seizures were intractable to multiple antiepileptic drugs. Brain MRI showed left hippocampal sclerosis. Interictal cerebral SPECT showed a relative hyperperfusion area over the left hemisphere. Interictal surface EEG was non-lateralising but ictal EEG disclosed a right hemispheric onset. On withdrawal of antiepileptic drugs, seven complex partial seizures with secondary generalised tonic clonic seizures were recorded within a period of 72 hours. His usual antiepileptic drugs were then restarted. Thirty hours after his last secondary generalised tonic-clonic seizure, he began to develop emotional lability, talking nonsense, restlessness, auditory hallucination, persecutory delusion, and delusion of superstition. Cerebral SPECT study, performed 2 days later while his psychotic features persisted, showed two relative hyperperfused areas over the right temporal neocortex and contralateral basal ganglion in addition to the original hyperperfused area over the left hemisphere. An antipsychotic agent (thioridazine) was...
started after the cerebral SPECT. His psychotic symptoms resolved 2 weeks later without full recovery.

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

Both patients showed postictal psychosis and had a regional increase in rCBF over the right temporal neocortex and the left basal ganglia compared with their interictal study (figure). Quantitative analysis for patient 1 showed decreases 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 PP and IP over right MT was −3.8% (13.14217 to 12.64158); over right LT was +178.6% (10.4696 to 18.70027); and over left BG was +155.9% (5.85556 to 3.27522).

Postictal psychosis is a distinct clinical event associated with temporal lobe epilepsy.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 cluster of complex partial seizures. Partial seizures were induced by abrupt withdrawal of antiepileptic drugs.7 The cluster occurs in patients with poorly controlled seizures. The clinical course of postictal psychosis is usually benign and predictable.8 In our patients, the duration of psychotic disturbances lasted from 10 to 14 days, which is in keeping with the majority of cases.9 The clinical course of postictal psychosis is usually benign and predictable.8 In our patients, the duration of psychotic disturbances lasted from 10 to 14 days, which is in keeping with the majority of cases.9

The underlying mechanism of postictal psychosis is unknown. Postictal cerebral hypofunction has been postulated as an analogy to Todd’s paralysis after seizure.1,2 However, the presence of increased rCBF during postictal psychosis, may suggest an alternative explanation as ictal SPECT has been shown to be highly sensitive and specific for ictal events.3,4

Oncocetal 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.5

Previous research from this laboratory disclosed that peculiar isoforms of fibronectin (FN) and tenasin (TN) typically occur in fetal and neoplastic tissues.6,7 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 oncocetal 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 manifesta-

tion of their disease. There was no drug history before bleeding. Control specimens from two right gyri recti and one cerebellar tonsil were obtained, respectively, from operations for ruptured aneurysms of the anterior communicating artery or for Arnold Chiari malformation.

Immunohistochemical evaluations were performed on 5 μm thick cryostat sections using a protocol reported previously.8 Owing to the limited amount of available material, only in a few cases was some fresh tissue retained to allow western blots. Distribution of FN and TN isoforms was investigated using three monoclonal antibodies (mAbs) or two Ab fragments, obtained by phage display technology, respectively. These Abs, prepared in our laboratory, were found to work on fresh frozen material. According to the previous 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). Control sections were processed identically to the other specimens, but the primary antibody was substituted with a specific immunoglobulin of recombinant antibodies. The antibodies were blocked using the specific antigens. The antibodies were blocked using the specific antigens. The antibodies were blocked using the specific antigens. The antibodies were blocked using the specific antigens. The antibodies were blocked using the specific antigens. The antibodies were blocked using the specific antigens. The antibodies were blocked using the specific antigens. The antibodies were blocked using the specific antigens. The antibodies were blocked using the specific antigens. The antibodies were blocked using the specific antigens. The antibodies were blocked using the specific antigens. The antibodies were blocked using the specific antigens. The antibodies were blocked using the specific antigens.
The presence of angiogenic features in AVMs might result from maintenance of proliferating and remodelling potentials, or from a specific response to haemodynamic stress in vascular structures subjected to increased blood flow and pressure. Occurrence of these features also in vessels lying in areas peripheral to the nidus might be related to recruitment of the neighbouring vasculature, possibly dependent on focal ischaemia in the setting of arteriovenous shunting. However, the presence in apparently normal vasculature of molecules typically occurring in fetal tissues and malignancies indicate that cerebral AVMs may not be static lesions. Further studies are needed to ascertain whether this phenomenon results merely from haemodynamic stress or actually reflects an intrinsic growth potential. Should this second be the case, current therapeutic strategies would possibly require revision.

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

Hashimoto’s encephalopathy presenting as “myxoedematous madness”

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

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

A 63 year old market stallholder without medical or psychiatric history was brought to a local psychiatric hospital by the police. His business had been in decline for several months, and his family had noticed uncharacteristic emotional lability. In the weeks preceding admission he had experienced delusions and hallucinations, and exhibited constantly fearful and withdrawn. On the day of admission he had made a bonfire in the garden and burned his wife’s clothes, family photographs, furniture, and business papers. When his wife and son tried to intervene he
became aggressive and threatened them with a saw. The general practitioner was called and suspected that he had a new psychological or a severe depressive illness. Police assistance was requested because of the patient's continuing violent behaviour.

On admission he was unkempt but cooperative and appeared to have an increased or depressed mood. He denied depression, but displayed no insight into the irregularity of his behaviour. No psychotic features were seen, although during the admission he consistently rationalised all reported psychiatric phenomena. He was aggressive towards staff and made repeated attempts to abscond. General physical examination was unremarkable. Neurological examination was normal except for spoken language, which was fluent and grammatical, but contained word finding pauses, circumlocutions, and occasional semantic errors (for example, “I just want to get my feet back on the table”). Formal neuropsychological testing, and a screen of laboratory tests for reversible causes of encephalopathy, were performed on admission, and results are presented below (column A). Attention is drawn to his mild naming deficit, and poor performance on the Rey figure, which was due to planning rather than visuospatial ability. Therefore, there is no evidence of increased antimicrosomal antibodies and normalisation with thyroxine replacement alone.4

The mild and relatively circumscribed neuropsychological deficits coupled with florid psychotic phenomena, also contrast with the profound global disturbance of cognition usually associated with Hashimoto's thyroiditis.3 This distinction suggests that microvascular disruption and thyroid hormone depletion may emphasise different aspects of the clinical range in Hashimoto’s disease, the most common being cognitive and affective change.5

In summary, therefore, this patient presented in clear consciousness with a first episode of acute psychosis, and evidence of subtle executive and linguistic neuropsychological disturbance, on the background of gradual behavioural and affective change. He was profoundly hypothyroid due to an autoimmune thyroiditis, but there was no clinical evidence of thyroid failure other than the abnormal mental state. The psychiatric component of his illness recovered fully, and the antithyroid microsomal antibody titre fell 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, athetosis, 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 rapid 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, athetosis, hemiballism, and dystonia.1 We report on a patient with CJD who manifested with an alien hand.

Alien hand sign in Creutzfeldt-Jakob disease

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

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Alien hand is a rare and striking phenomenon defined as “a patient's failure to recognise the action of one of his hands as his own”.2 One of the patient's hands acts as a stranger to the body and is uncooperative. Thus, there is loss of feeling of ownership but not loss of sensation in the affected hand. Originally described in callosal tumours, the aetiology of alien hand also includes surgical callosotomy,3 infarction of the medial frontal cortex, occipitotemporal lobe, and subdural infection,4 and corticobasal degeneration.5,6

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

Table 1 Laboratory and neuropsychological results at presentation (A) and at 12 month follow up (B)

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<tr>
<th>Laboratory (units)</th>
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<tr>
<td>Full blood count</td>
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<tr>
<td>Erythrocyte sedimentation rate</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>Urea and electrolytes</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>Liver function tests</td>
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<td>Acute phase reactant</td>
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<td>Negative</td>
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<tr>
<td>B12 and folate</td>
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<tr>
<td>VDLR</td>
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<tr>
<td>Thyroid stimulating hormone (mU/L)</td>
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<td>Not tested</td>
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<tr>
<td>Free T4 (pmol/L)</td>
<td>1:25600</td>
<td>1:1600</td>
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<tr>
<td>Antithyroid microsomal antibody titer</td>
<td>25/30</td>
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<td>Antithyroid peroxidase antibody titer</td>
<td>1:1600</td>
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<tr>
<td>WAIS-R (performance)</td>
<td>25</td>
<td>11</td>
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<tr>
<td>WAIS-R (verbal)</td>
<td>23</td>
<td>6</td>
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<tr>
<td>FAS verbal fluency (&gt;30)</td>
<td>75%</td>
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<tr>
<td>Rey-Osterreith complex figure (recall)</td>
<td>80%</td>
<td>30%</td>
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<td>Rey-Osterreith complex figure (copy) (36)</td>
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<td>NART IQ</td>
<td>18th percentile</td>
<td>10th percentile</td>
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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 conscious, hallucinations, by halitosis. The effect was sad and he had partial insight for his mental dysfunction. He was disoriented for time, place, and situation. He could understand speech and was able to follow instructions involving two consecutive components. Naming was preserved. Prominent dysgraphia 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, hematologic, and sedimentation rate were normal, as were folic acid, vitamin B12 concentrations, and thyroid function. Venereal disease research laboratory and HIV tests were negative. The cerebrospinal fluid had normal content. Brain CT showed mild cerebral atrophy. An EEG showed severe diffuse slowing at admission. Within a week, repeated EEGs showed triphasic waves with a periodic pattern of 1-1.5 Hz.

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

This short fatal neurological disease manifested by fulminant dementia, myoclonic jerks, and extrapyramidal and cerebellar dysfunction was strongly suggestive of CJD. The periodic EEG pattern reinforced this diagnosis. Our patient’s alien hand was part of the otherwise characteristic clinical picture of CJD, but occurred early in the 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...wanndered out of her view”. In the second, the alien arm performed complex actions such as unbottling 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 or stimulus sensitive myoclonus, spastic hemiparesis, and cortical sensory loss.

The literature seems to describe distinct forms of alien hand. All share the occurrence of involuntary movements contrary to the patient’s stated intent, but the types of movement differ. In the callosal form, there are purposeful movements of the non-dominant hand. In the frontotemporal form, there is grasping and utilisation behaviour of the dominant hand. In the corticobasal degeneration, there are aimless movements of either hand. When a consequence of a primary or vascular pathology, alien hands can perform complex acts such as trying to tear clothes or undoing buttons. The description by MacGowan et al has characteristics of the callosal form (especially in patient 2). However, our case suggests that the alien hand sign in CJD may appear in a different type, performing less complex movements which resemble those reported by Riley et al in corticobasal degeneration. These authors described the alien limb as “involuntarily rising and touching the mouth and eyes” (patient 1). The patient thought that she “was powerless to stop this movement” and when directed to stop responded that “she can’t”. Another patient’s left arm was at times “elevated in front of him”, while he was “unaware of this situation until his attention was called to it” (patient 2).

Another related phenomenon coined as “arm levitation” was reported in progressive supranuclear palsy. In these patients the arm involuntarily raised and performed semi-purposeful movements.

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

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

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

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

basic protein were not tested. Nerve conduc-
tion studies were consistent with a predomi-
nately motor demyelinating peripheral neu-ropathy (table). Her symptoms improved spontaneo-
usly and she was discharged home after 2 weeks. For 2 years she was asympto-
matic on a gluten free diet.

At the age of 12 she presented acutely with
severe abdominal pain 8 days after a weekly
intake of bread meant to be gluten free. Two
weeks later, due to persisting gastrointestinal
symptoms, her parents excluded the bread
from her diet. After 2 further weeks, while
the abdominal pain was gradually improving, she
had a new episode of acute weakness in the
lower limbs and sensory abnormalities in-
cluding burning paraesthesiae. On neurologi-
cal examination the legs showed marked
diminution in muscle power; absent deep
tendon reflexes, and a reduction in pain and
temperature; light touch, perception of posi-
tion, and vibration were preserved. Walking
was impaired and the patient was bedridden.
Otherwise the examination was normal.
A haemogram showed white cell counts of
9700/mm³. 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 lumbar puncture or nerve biopsy.

Over the next 2 weeks her neurological dis-
abilities spontaneously improved until full
cognition 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 prev-
iously reported. In the paediatric age group,

*Electrophysiological study suggestive in both episodes of an acute demyelinating peripheral neuropathy confined to the lower limbs. Values were within normal limits as the upper limbs.*

<table>
<thead>
<tr>
<th>1st Episode</th>
<th>2nd Episode</th>
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<tr>
<td><strong>Peroneal</strong></td>
<td><strong>Tibial</strong></td>
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<tr>
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<td>26</td>
</tr>
<tr>
<td>DL (ms)</td>
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</tr>
<tr>
<td>F wave latency (ms)</td>
<td>70</td>
</tr>
<tr>
<td>CMAP (µV)</td>
<td>3</td>
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<tr>
<td>SGV (µV)</td>
<td>42</td>
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<tr>
<td>AMP (µV)</td>
<td>38</td>
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<td>SGV (µV)</td>
<td>42</td>
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<td>AMP (µV)</td>
<td>38</td>
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MVC=motor conduction velocity; DL=distal latency; CMAP=compound motor action potential; SGV=sensory conduction velocity; AMP=amplitude; L=left; R=right.

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 sensitisation to gluten at least at the time
of diagnosis, in the clinical practice at follow up,
during a gluten challenge, pathological values
of these antibodies may not be detected. In
the present case the time course of the disease
might be suggestive of an antibody mediated
response. However, we could not detect any
pathological concentrations of AGA, EMA,
or ARA antibodies either during the course of
the disease or at follow up.

It is known that in celiac disease many
immunological perturbations can occur out-
side the gastrointestinal tract. Crossing of
the antigens through a damaged small intestinal
mucosa, deposition of immune complexes in
target organs, a reduction in immune surveil-
ance, mechanism of molecular mimicry, and
activated T cell response may contribute to
the pathogenesis of the diseases associated
with celiac disease. Direct toxic effects of
gladin 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, the present case shows two major
issues: an acute polynuropathy 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.

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

In the present study, the prevalence of primitive reflexes was highest in the twenty-five patients with peripheral vascular disease and a non-vascular control group. Independent predictors of these reflexes were also examined in peripheral vascular disease. Both groups were drawn from the same geographical 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-

Twenty five consecutive non-ambulates on the waiting list for femoropopliteal bypass operation were compared with 25 post-operative patients who had undergone elective hip or knee replacement and were in rehabilitation. All participants were aged 65 and over at the time of intervention. Patients with peripheral vascular disease all had clinical and Doppler proved evidence of peripheral 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. All subjects were
examined using a rating scale for the evaluation 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 diagnos-

in the relation between peripheral and central vascular pathology.

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

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*Higher mean score in people with peripheral vascular disease.

Small numbers of patients, which may also have obscured other significant findings, between the two groups, limit the present study. However, there is some evidence that clinically relevant cerebrovascular disease may accompany peripheral vascular disease and that recurrent dissection 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, fur-

in the investigations performed at the transfer-

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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 EEG 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, “anxiety”, “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 actiology was not specifically addressed—tha is, tests designed to detect malingering during neuropsychological testing were not administered by the examiner, who had not been informed at the time of consultation of the presumptive neurological diagnosis of malinger- ing 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 symmetric and plantar responses downgoing. He drew a clock normally at the 1 year follow up.

The clinical and laboratory findings described above indicate beyond any doubt the non-organic nature of this patient’s left hemiplegia/hemianaesthesia. 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 neuropsychologist’s perspective, typically associated with parietal lobe dysfunction, usually of the non-dominant hemisphere, especially if associated with left hemispatial neglect. To our knowledge, this is the first reported case of factitious clock drawing and constructional apraxia. Bedside mental status testing also demonstrated the more common simulated deficits of impaired attention and absent three word recall. In retrospect, the severe neglect on clock drawing was perhaps “too good to be true”, especially in the light of the near normal line bisection demonstrated on the same day. The mirror image distortion of the house was also very unusual and, furthermore, the mirror reversal itself is evidence of lack of clinical neglect. The distortion of the house, 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 stress, 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 symp- tomatology just as he was scheduled for return to work after his first non-organic hemiplegic episode, and the intentionality required to feign poor clock drawing and constructional apraxia, there is much to support a diagnosis of malingering. Nevertheless, classification as a factitious disorder is at least as justifiable in view of the patient’s willingness to undergo medical investigations, including video monitoring.

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

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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, putaminal 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


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appropriately. Neurological examination showed contralateral gaze preference, supra-nuclear vertical gaze palsy, difficulty converging, left sided flaccid hemiparesis, and dense, left sided hemianesthesia. Deep tendon reflexes were absent on the left and Babinski’s response was extensor to the left. He had a left sided weakness, he 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 interested in hearing the nurses’ admission for closer observation. He told the nurses that someone else’s arm was in his bed. On one occasion, holding up his left arm with his right, he told the nurses 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. He was then consciously recalled being otherwise. 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 incomplete recovery. Simple attention was intact, but attentional changes. Brain CT 30 days after stroke showed, in a patient with severe hemiparesis, moderate cerebellar atrophy and mild to moderate prominence of the frontal cortical sulci compatible with cerebellar atrophy.

Structural MRI performed 44 days after the stroke showed a 2 cm area of absent cerebral blood volume at the posterior margin of the right thalamus without any evidence of decreased cerebral blood volume within the right parietal, frontal, or temporal cortex.

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

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

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

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

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

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Epileptic cardiac arrest

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

Cardiac arrhythmias subsequent to epileptic seizures have been recognised for more than 50 years. They provoke diagnostic confusion and may be a mechanism of sudden unexplained death in epilepsy. Whereas sinus tachycardia was noted to accompany more than 90% of epileptic seizures, isolated bradycardia was seen much
less commonly (only 1 of 74 seizures recorded). A review in 1996 of the “ictal bradycardia syndrome” showed only 15 documented cases in the literature of either bradycardia or asystole associated with seizures. Most patients had temporal lobe seizures. The longest duration of asystole previously reported is in a 17 year old man with temporal lobe epilepsy who sustained a 22 second pause in cardiac output. More typically the asystolic periods in documented cases are in the region of 5–10 seconds. Shorter duration asystole may not compromise cerebral function sufficiently to cause loss of consciousness. Implantation of a cardiac pacemaker is advocated but does not ensure that lapses of consciousness are eliminated if these are directly related to the seizure rather than to the secondary asystole. We report on a patient with epileptic cardiac asystole of 25 seconds duration demonstrated by prolonged simultaneous EEG/ECG monitoring which responded well to pacemaker insertion.

A previously well 34 year old right handed builder was referred with a 1 year history of fortnightly episodes of loss of consciousness. There was no associated warning, aura, chest pain, or palpitations and the patient was only aware of the episode once consciousness was...
restored and he found himself lying on the floor. On recovery there was no confusion, drowsiness, dysphasia, or diuresis. Often, however, he sustained soft tissue injuries to his face and scalp.

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

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

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

Cardiovascular and neurological examination was normal, as were MRI and routine interictal EEG. Sixteen channel ambulatory EEG using an Oxford Instruments digital EEG receiver was performed continuously for 340 hours before an episode was captured. Interictally rare spikes were seen over the right frontocentrotemporal region during sleep. The onset of the episode was not witnessed and the patient was found on 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, his first 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 lasting 10 seconds (figure B). After a few seconds of bradycardia then asystolia, sinus rhythm was restored. Throughout the episode the QT interval on the EEG remained within normal limits. The EEG 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 a large amplitude generalised rhythmic <1 Hz activity became apparent. Diffuse theta activity was seen for a further 15 seconds before the EEG returned to its resting state.

A VFI 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 dysrrhythmias are an uncommon but serious consequence of partial seizures. Our case is unusual because of the duration of the episode, of a series of 26 patients with 74 temporal lobe seizures in which simultaneous EEG and ECG recordings were acquired, ictal arrhythmias occurred in 52% of seizures, the commonest being irregular abrupt changes in heart rate, (both acceleration and deceleration) occurring towards the end of the period of EEG abnormality. Interictally, patients with epilepsy seem no more likely than age and sex matched healthy subjects to experience arrhythmias although in one study patients with epilepsy had a faster ventricular rate and a longer QT interval than controls.1 It has been hypothesised that there is laterisation with respect to central autonomic cardiac control with an increase in heart rate seen after an increase in sympathetic activation of monoamines and inactivation of the left hemisphere and a decrease in heart rate on right hemispheric inactivation. Experimental stimulation of the rostral posterior insular cardiac arachnoid and a secondary central arachnoid is possible only with simultaneous EEG/ECG recordings.

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

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant disorder, the molecular basis of which is a 1.5 Mb deletion in chromosome 17p11.2 including the peripheral myelin protein-22 (PMP-22) gene.1 HNPP typically presents recurrent pressure palsies of peripheral nerves, such as the axillary, median, radial, ulnar, or peroneal nerves, at common entrapment sites. Respiratory muscle weakness has not been previously reported in HNPP. We describe a patient with HNPP who presented with respiratory failure and proximal muscle weakness who were prominent features.

The patient started to have dypsania 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 acute respiratory failure and proximal muscle weakness. The patient was a comatose 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 hypoventilation.

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

In a neurological examination, the patient’s mental state and cranial nerves were normal. Evidence of muscular atrophy was not found. The patient was acomatose 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 hypoventilation.

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of myelinated fibres was reduced (5726/mm³ normally thin axonal myelin sheaths. The density of the myelin sheath and some abnormalities were rare. A left sural nerve unit potentials of long duration, but denervation potentials were rare. A left sural nerve showed polyphasic motor biceps femoris, tibialis anterior, and gastrocnemius muscles showed polyphasic motor unit potentials of long duration, but denervation potentials were rare. A left sural nerve biopsy showed scattered tomacular thickening of the myelin sheath and some abnormally thin axonal myelin sheaths. The density of myelinated fibres was reduced (5726/mm³).

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

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

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

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

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

General muscle atrophies, which are most prominent in the trunk are shown. A tracheotomy was performed for nocturnal hyperventilation because the patient required mechanical respiratory support during the night.

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

Spinal accessory neuropathy and internal jugular thrombosis after carotid endarterectomy

Spinal accessory neuropathy is a rare complication of carotid endarterectomy (CEA). Internal jugular venous thrombosis after CEA has also been reported rarely, but is likely more common; as internal jugular
Venous thrombosis is often asymptomatic, or presents with non-specific pain, it is probably unrecognized 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. Electodiagnostic studies were consistent with partial right accessory neuropathy with minor denervation of the right trapezius. Cervical ultrasonography and MRI demonstrated right internal jugular venous thrombosis. The patient was treated with a shoulder support, analgesics, and low dose aspirin. There was no significant clinical change 1 year after CEA. Repeat electrodagnostic studies were consistent with chronic right spinal accessory neuropathy, and repeat ultrasonography showed persistent right internal jugular venous thrombosis.

Spinal accessory neuropathy was first reported as a complication of CEA in 1982.\(^1\) Since then, there have been several case reports and small series.\(^2\) A 1996 review of reports of cranial neuropathy after CEA disclosed only one patient with spinal accessory neuropathy in over 3000 cases.\(^1\) Although the authors did not include several other reports\(^3\) which, taken together, may seem to suggest a somewhat higher incidence, the overall small number of reported cases in proportion to the hundreds of thousands of CEsAs that have been done worldwide suggests that clinically significant spinal accessory neuropathy is a rare complication. Minor right spinal accessory neuropathy after CEA may be more frequent. The cause of spinal accessory neuropathy after CEA is usually not well established, but intraoperative nerve stretching or compression from retraction is most often invoked.\(^4\) Delayed onset (after 3 weeks) has been noted in some; for these patients, postoperative inflammation and scarring seem more likely causes. Spinal accessory nerve transection or ischemia/infarction (arterial or venous) are other possibilities. As in our patient, high carotid dissection and retraction have been reported to precede spinal accessory neuropathy.\(^5,6\)

The spinal accessory nerve courses along the internal jugular vein and near the internal carotid artery, typically well above the carotid bifurcation. This may explain that a high carotid 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 unknown.

From our search, internal jugular venous thrombosis after CEA has been reported in only one case.\(^7\) As Southcott et al noted, retraction of the internal jugular during CEA may cause complete occlusion, leading to thrombosis from venous stasis or endothelial injury. Other causes of internal jugular venous thrombosis include jugular cannulation, blunt cervical trauma, and a hypercoagulable state. Internal jugular venous thrombosis may occur even up to a week after neck dissection, often with recanalisation after several months.\(^8\)

The presence of induration about the incision site and a palpable supraclavicular cord in our patient led us to suspect venous thrombosis. Internal jugular venous thrombosis may be asymptomatic. Potential symptoms of internal jugular venous thrombosis include headache, dysphagia, and anterolateral neck pain, tenderness, and swelling. In addition to paresthesia, fever and leukocytosis may occur.\(^9\) Common pathogenetic mechanisms for spinal accessory neuropathy and internal jugular venous thrombosis may include intraoperative traction, haematoma, and postoperative inflammation and scarring.

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

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

We report the first case of extensive cerebral infarct in a young sportsman consuming high doses of MaHuang extract and creatine monohydrate for body building.\(^1\) The cause of the stroke is likely to be drug induced, although some concomitant factors may have contributed.

A 33 year old man had a severe aphasia on awakening in the morning of 23 January 1994. He did not complain of other symptoms. He was referred to our department on 26 January 1999. He had a Wernicke aphasia with a slight right sided face and arm weakness and a right Babinski sign. His blood pressure was 140/60 and his pulse 54 per minute. Brain CT showed signs of extensive left middle cerebral artery infarct. Cervical ultrasound duplex scanning and cerebral angiography were normal. Cerebral CBF examination and EEG were also normal except for a patent foramen ovale.

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

Although a paradoxical embolism through a patent foramen ovale in this patient cannot be ruled out as he recently went on a transatlantic air flight, there was no deep venous thrombosis and D-dimers were normal. However, ephedrine has an indirect sympathomimetic action and is responsible for arteriolar vasoconstriction in addition to other catecholaminergic effects. Both ischaemic and haemorrhagic stroke associated with ephedrine use have been reported.\(^2\) Acute myocardial infarction and acute psychosis have also been reported after taking ephedrine and other sympathomimetic drugs.\(^3\) Ephedrine and its metabolites are natural products that are used in non-prescription remedies for multiple uses including weight loss in a tobacco use. This contains ephedrine, is used among young sportsmen and sportswomen as an energy supplement in non-prescription tablets in some countries.

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

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

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

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Petroclival meningioma as a cause of ipsilateral cervicofacial dyskinesias

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

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

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

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

An MRI study showed a large gadolinium enhancing tumour within the left cerebello-

pontine angle extending to the cavum Meck-

eli with marked displacement of the brain-

tem to the contralateral side (figure A and B). Mesencephalic angiography showed a discrete blush of the tumour as typically seen in menin-

giomas. The tumour was totally removed by a combined transpetrosal supratentorial and infratentorial presigmoidal approach. The postoperative course was uneventful and there were no new deficits. The facial palsy improved slightly as well as the trigeminal hypeaesthesia. Audiometry remained un-

changed. Postoperative imaging showed no residual tumour and the displacement of the brain stem within the posterior fossa had resolved (figure C). Marked improvement of the left sided craniofacial dyskinesias oc-

urred during the next weeks.

The postoperative improvement of the dys-
tonic and choreic grimacing and the cervical dystonia indicates a causal association between the petroclival meningioma and the segmental hyperkinetic movement disorders. Such a rela-
tion is supported also by the absence of a fam-

ily history of movement disorders and the absence of previous exposure to neuroleptic medication. Hyperkinetic movement disorders due to tumours of the brain stem or of the pos-
terior fossa have been reported only rarely. Asymmetric blepharospasm was recently found in a patient with an ipsilateral mesencephalic cyst.6 Hemifacial spasm was seen in patients with paroxysmal neumonias, monomi-

omas, and epidermoid tumours of the cerebel-

lopontine angle.7 Acoustic neuromas and anaplastic pontocerebellar glioma can be asso-

ciated with facial myokimia and spastic paretic facial contracture.8,9 Cervical dystonia due to tumours of the cerebellopontine angle have been reported recently.10

The pathophysiological mechanisms re-

sponsible for dystonic movement disorders con-

cerned with central or functional lesions of the brainstem are not fully understood. The possibility of denervation supersensitivity of cranial nerve nuclei has been proposed previ-

ously. Alternatively, enhanced excitability of brain stem interneurons has been suggested. This pathophysiological mechanism is sup-

ported by the findings of blink reflex studies in patients with blepharospasm, spasmodic dysphonia, and cervical dystonia. Tolosa et al.11 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 close temporal relation between as-

sumption of dialysable leucocyte extract therapy and appearance of cerebral white matter lesions in our patient supports the possibility that the association of the two events might not be casual. Despite the absence of biopsy, we reasonably exclud

Acute multifocal cerebral white matter lesions during transfer factor therapy

Transfer factor is an active substance of unknown strenght present in dialysable leuc-

cyte extract which is assumed to transfer cell mediated immunity in an antigen specific fashion.12 The mechanisms of action of trans-

fer factor are still far from clear; in vitro dial-

ysable leucocyte extract increases macro-

phage activation and interleukin (IL) 1 produ-

cion and enhances leucocyte chemo-

taxis and natural killer function. Transfer fac-

tor has been reported to stimulate the cell mediated antigen specific response in patients with various infections13; therefore, treatment with transfer factor has been suggested in patients with selective deficits in cell medi-

ated immunity such as some refractory ne-

oplasms and chronic infections. Moreover, it has been used in the treatment of uveitis.14 Administration of dialysable leucocyte extract has seemed to be free of hypersensitivity, long lasting side effects, or complications, except for transitory hyperpyrexia.15

We report on a patient in whom multiple cerebral white matter lesions developed after taking dialysable leucocyte extract orally for uveitis. A 28 year old man was admitted to hospital because of headache, mental confu-

sion, and right hemiparesis. He had had recur-

rent bilateral uveitis from the age of 12 to 14 with right relative sight in right eye. In January 1995 retinal vasculitis was diagnosed at fundoscopy and in July 1995 he started oral transfer factor as dialysable leucocyte extract twice a week. He complained of gen-

eralised 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, Babinski’s sign. No fever or meningismus was present.

Laboratory examinations on admission showed a slight increase in total serum protein (8.4 g/l, normal 6.0–8.0 g/l, although the serum protein fraction was normal), antistreptolysin titres (355 UI/ml, normal <200 UI/ml), and anticardiolipin IgG (30 UI/ml, normal <12 UI/ml). 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 titres (265 UI/ml). Two MR scans at 1 and 4 months after onset showed progressive reduction of lesions without contrast enhancement. A final MR scan 20 months after onset showed further regression of lesions with 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.

In summary, we found a case of acute multifocal cerebral white matter lesions in an elderly patient which did not show contrast enhancement. A close temporal relation between as-

sumption of dialysable leucocyte extract therapy and appearance of cerebral white matter lesions in our patient supports the possibility that the association of the two events might not be casual. Despite the absence of biopsy, we reasonably exclud


3 Krauss JK, Wählho P, Scheremet R, et al. Facial myokimia and spastic paretic facial con-

tracture as the result of anaplastic pontocere-


4 Krauss JK, Seeger W, Jankovic J. Cervical dysto-


61–9.
the diagnosis of vasculitis or neuro-Bechet’s disease although in the absence of biopsy. In fact, the clinical, laboratory, and MRI findings were not typical and a low titre of anticardiolipin antibodies is found in 2% of healthy subjects. The occurrence at different time of focal cerebral white matter lesions highly supports the diagnosis of multiple sclerosis, but some clinical and laboratory findings in the our patient are not typical for this condition. Mental confusion is not common at the onset of multiple sclerosis whereas it is often found in acute disseminated encephalitis. In addition, CSF without oligoclonal banding argues against a diagnosis of multiple sclerosis, whereas it is commonly found in acute disseminated encephalitis. On the other hand the possibility that acute disseminated encephalitis may recur has been accepted and on the basis of the patient’s clinical picture and CSF, we favoured such a diagnosis.

The pathogenic mechanisms underlying the triggering, development, and duration of multiple sclerosis and acute disseminated encephalitis are still far from clear despite the progress made in unravelling them. Some findings suggest that acute disseminated encephalitis and multiple sclerosis lie at two poles of an autoimmune range, in which autoantigen reactivity is only temporary and on the basis of the patient's clinical picture and CSF, we favoured such a diagnosis.

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

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

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

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

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

According to medical history, the patient’s mother had received weekly injections of Depoprovera during pregnancy. A single child born after a normal term delivery, he underwent surgery for an inguinal hernia at 3 weeks. Developmental milestones were only moderately delayed. At 9 months, he walked 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, dysgraphaesia on sensory testing, and a manneristic gripping handshake. There were no extrapyramidal movements, dysarthria, or parkinsonism. He spoke at 2 years with poor articulation, and still speaks in short, unelaborated sentences. He underwent surgery for an inguinal hernia at 3 weeks. Developmental milestones were only moderately delayed. At 9 months, he walked 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.

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

The craniovertebral junction can be affected by several pseudotumorous masses extradurally located, such as rheumatoid panus, hypertrophic non-union of odontoid fracture, post-traumatic cicatrix, synovial cysts, tumorous calcium pyrophosphate dihydrate crystal deposition, tophaceous gout, calcification of the posterior longitudinal ligament, synovial disease-like pigmented villonodular synovitis, and synovial chondromatosis. Hypertrophy of the atlantoaxial ligaments as a consequence of degenerative disease was recently recognised as an individual entity. Only five previous cases have been published. We add another case to the short series available in the literature, emphasising that as the cause of the spinal cord compression is amenable to surgical removal, symptomatic patients should be diagnosed and treated without delay.

A 66 year old woman presented with a rapid development of progressive spastic tetraparesis and an unremarkable medical history. There was no osteosclerosis or instability on plain cervical radiography and CT. A bone scan with "Tc was unremarkable. Magnetic resonance imaging showed a retro-odontoid extradural mass that was homogeneous and isointense on T1 weighted signal, demonstrating no enhancement after intravenous gadolinium contrast, and was compressing the upper cervical spinal cord (figure). The laboratory tests were normal, confirming the absence of rheumatoid arthritis, metabolic disease, or gout. Surgical removal via a transoral approach with a minimal bony resection was direct and provided sufficient space to obtain spinal cord decompression. It was followed by a posterior C1-C2 fusion. Microscopically, the lesion had no capsule and resembled a hypertrophic ligamentum flavum. Microscopically, it was non-inflammatory, hypocellular, and ligamentary tissue found within the mass appeared fibrous and almost disintegrated. The patient regained normal neurological function. Over a 3 year follow up period there was no recurrence.

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

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

A 63 year old woman who fell off her bicycle had a left temporal region head injury with evidence of initial loss of consciousness of 5 minutes and scalp excoriation of that area. On arrival at our hospital 30 minutes later she was alert and oriented. Cranial nerve functions, including extraocular motion and hearing function, were preserved. Pain and temperature sensations of the right side, including her face, showed a 70% decrease compared with the left side; however, position and vibration sensations were normal. Other neurological examinations, including motor function, coordination, and deep tendon reflex, were normal. The patient’s only complaints were left temporal headache and right hemihypaesthesia. Brain CT on admission showed a discrete and linear high density at the left ambient cistern and linear high density at the left ambient cistern without other intracranial lesions. On neurological literature, almost always ac-

able lesions for sensory impairment, detectable by neuroimaging studies, were reported. One study found that the lateral and ventral spinothalamic and ventral trigeminothalamic tracts pass at the surface of this level by carrying a superficial somatosensory input. The lesion shown in our MR images seemed to be localised to these tracts. The medial lemniscus for the deep sensation and lateral lemniscus and nucleus of inferior colliculus associated with hearing function from ventral to 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. Injury of the midbrain was the surface of the midbrain; however, due to the proximity of the tentorial edge to the midbrain on the injured side, tentorial contact to the midbrain supposedly occurred more readily. Brain MRI findings support the anatomical features of this tentorial coup injury. This injury is not rare in patients with severe head injury, accompanied by other intracranial lesions, and is often caused by lateral displacement of the brain stem relative to the tentorium. It is influenced by congenital variation in the size and shape of the tentorial incisura. The brain stem of the patient with a narrow incisura is more vulnerable to the direct contusive effects than that of a patient with a wider incisura. Therefore, even in minor head injury, this mechanism may occur in patients preconditioned with narrow tentorial incisura, which may have been the case in our patient.

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

The MR images in our case showed a discrete lesion at the dorsolateral midbrain. Topographical study at this lower midbrain level showed that the lateral and ventral spinothalamic and ventral trigeminothalamic tracts pass at the surface of this level by carrying a superficial somatosensory input. The lesion shown in our MR images seemed to be localised to these tracts. The medial lemniscus for the deep sensation and lateral lemniscus and nucleus of inferior colliculus associated with hearing function from ventral to 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. Injury of the midbrain was the surface of the midbrain; however, due to the proximity of the tentorial edge to the midbrain on the injured side, tentorial contact to the midbrain supposedly occurred more readily. Brain MRI findings support the anatomical features of this tentorial coup injury. This injury is not rare in patients with severe head injury, accompanied by other intracranial lesions, and is often caused by lateral displacement of the brain stem relative to the tentorium. It is influenced by congenital variation in the size and shape of the tentorial incisura. The brain stem of the patient with a narrow incisura is more vulnerable to the direct contusive effects than that of a patient with a wider incisura. Therefore, even in minor head injury, this mechanism may occur in patients preconditioned with narrow tentorial incisura, which may have been the case in our patient.

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

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We read with interest the article by Miyagi et al and comment on the medical treatment of toluene induced tremor. Microdialysis experiments in rats have shown that inhalation of toluene increases extracellular γ-amino butyric acid (GABA) concentrations within the cerebellar cortex which probably explains why GABA agonists including benzodiazepines (for example, clonazepam) are not very effective in toluene induced tremor and ataxia. Rat experiments also showed a 50% reduction in brain catecholaminergic neurons. Denervation of certain cerebellar pathways is probably responsible for the loss of this dopaminergic innervation. Dopamine agonists could therefore be of potential interest in the treatment of toluene induced tremor. This hypothesis was explored in a recently described case, which showed remarkable clinical and iconographic similarities with that described by Miyagi et al: (a) long history of chronic toluene inhalation, (b) marked postural tremor, (c) progressive worsening of the symptoms despite abstinence from inhalant misuse, and (d) mild cerebral atrophy and marked low signal intensity in globus pallidus, thalami, red nuclei, and substantia nigrae on T2 weighted MRI. As our patient’s tremor was progressive, medical treatment with a dopamine agonist was considered. One particular agent (amantadine) caught our attention because it had proved successful in the treatment of postural tremor in patients of heredodegenerative disorders in which the dentatorubro-olivary system is affected. In addition, there is evidence that catecholaminergic pathways are also involved in this type of ataxias, supported by loss of dopaminergic neurons of these neurotransmitters in the CSF of patients with heredodegenerative ataxias. 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) which resulted in relapse of the tremor.

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

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

We think that there are two problems with this study that should make the physician cautious about accepting 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 astrocytomas and risk factors, and hence the positive predictive value of any screening tool in a general population of patients with tuberous sclerosis complex is likely to be different from those described in the highly selected group studied in this paper. The second point is that the authors have made a potentially misleading decision to exclude more than half their study sample because they do not have lesions close to the foramen of Monroe. It is not certain that all SEGAs arise from lesions close to the foramen. They may arise in the fourth ventricle. Furthermore, the late presentation of many lesions in the lateral ventricles has, in the past, precluded accurate determination of their point of origin. We therefore select 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 Monroe”. Inclusion of all patients 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 entered with gadolinium. The effect would be to remove the stated statistical significance (using Fisher’s exact tests) between the outcome and both of these explanatory variables.

Identifying the risk factors that can tell us which subependymal lesions will become invasive is important. As subependymal nodules and SEGAs seem to be histologically identical it is unlikely that pathologists will provide an answer. The study of Nabbout et al suggests some new hypotheses but does not state how many of the excluded 36 patients had no subependymal nodules or nodules that were not “near the foramen of Monroe”. Inclusion of all patients 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 entered 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.

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

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

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

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

Other terms used in the past refer to this form of ALS have been flaccid arm syndrome, suspended form, oranguatan 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 scapulohumeral form, or the chronic anterior poliomyelitis reported by Vulpian in 1886 and known in Franco-German literature as Vulpian-Bernhardt’s form of ALS.

At certain stages of the disease’s clinical course, it is probably difficult to differentiate it from progressive muscular atrophy (PMA). Some authors have said that PMA with late onset scapulohumeral distribution (over 45 years of age) generally leads to ALS as a matter of course.1

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

(1) The prevalence of this form of ALS constituted 10% of the ALS group as a whole (p = 0.05). (2) 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 higher median survival (a median survival of 57 months compared with 39 months in the ALS group).

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

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

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

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

Finally, we are in complete agreement that the presence of cervical spondylosis and ALS can cause difficulty in diagnosis. The problem lies in the fact that cervical spondylosis is a common condition. It is found in 83.5% of men and 80.7% of women over the age of 55. The faster progressive deterioration of the symptoms, the appearance of bulbar signs, and the absence of sensory symptoms and signs would favour the diagnosis of ALS.2


Isolated dysarthria

We read with interest the article by Urban et al. Using transcranial magnetic stimulation, the authors demonstrated electrophysiological evidence for a central monophasic of the tongue in patients with isolated dysarthria from stroke.1 As in their patients transcranial magnetic stimulation induced absent or delayed corticofugal responses at the tongue, the authors ascribed isolated dysarthria to interruption of the corticobulbar pathway, involving the thalamocortical and corticostriatal fibres as well as the corticobulbar fibres. In fact, lacunar infarctions around the internal capsule-corona radiata are likely to underlie these ascending and descending pathways.2

To assess corticopontocerebellar tract function, Urban et al investigated cerebellar blood flow in patients with isolated dysarthria using HMPAO-SPECT. They concluded that the corticopontocerebellar tract is preserved in isolated dysarthria because of no evidence for cerebellar diaschisis on SPECT. Their SPECT findings on cerebellar blood flow were similar to our results. However, we wonder whether cerebral cortical blood flow was preserved in their patients, because our SPECT study suggested frontal cortical dysfunction as underlying mechanism of isolated dysarthria. In our patients, maximal uptake of HMPAO was evident in three of seven patients reported by Urban et al and in two of 12 by us. This indicates that isolated dysarthria originates in incoordination of multiple organs necessary for speech articulation as well as a cortical component. Although interruption of the corticollingual 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:

Okuda et al draw attention to their article on pure dysarthria in Stroke1 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 the single lesions collected by us are more appropriate to correlate lesion topography with impaired function. The findings of Okuda et al are in line with our conclusion that interruption of the corticofugal pathway is a factor in the pathogenesis of dysarthria of extracerebral origin. Obviously, impairment of the corticofugal tract of one hemisphere by a single small lesion is an adequate condition for dysarthria. The patients of Okuda et al had more severe vascular disorder of the brain than our patients as can be concluded from the multiple infarctions. Thus, the bilateral frontothalamic hyperperfusion as disclosed by SPECT in the series of Okuda et al may be due to infarction in other parts of the brain compared with the lesion causing pure dysarthria.

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Motor cortical excitability in Huntington's disease

We read with great interest the paper of Hanajima et al2 reporting that intracortical inhibition of the motor cortex is normal in patients with chorea of various origins. At variance with the results we previously found3 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 studies1,2 may be due to differences in patient selection as they included patients with early stage Huntington's disease to “study the pathophysiology of chorea unaffected by other disorders movement.” They postulated that our cases, because of the reported correlation with a dyskinetic rating scale, had a more advanced stage of the disease possibly with coexisting dystonia or rigidity. These assertions deserve some comments.

The mean disease duration of our nine patients with Huntington's disease was 6.2 (4.1) years which is actually shorter than the duration of the six patients reported by Hanajima et al (8.3 (5.9) years). Most of our patients could be considered in an early stage of the disease, the Unified Huntington's disease rating scale, and none presented dystonia, rigidity, or any other additional movement disorder. In this regard, however, it should be pointed out that bradykinesia is often associated with chorea in patients with Huntington's disease4 and may even precede the appearance of choreic dyskinesias.5 Chorea itself is often reduced in the more advanced Huntington's disease5 stages.6 It is unlikely, therefore, that any neuropathological 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.7

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 of the disease as we did not find any change in four patients, two of them already reported,8 with positive DNA testing but completely asymptomatic.

The discrepancies between the two studies are more likely to be explained, at least in part, by some methodological differences. For instance, the amplitude of the control response was larger in our set (approximately 1.0 mV compared with 0.3 mV in the study of Hanajima et al). This may induce a different sensitivity of the test, and the amount of intracortical inhibition in our normal controls is greater (see also9) than in the study of Hanajima et al.

When interpreting the results of studies with paired transcranial magnetic stimulation pathophysio logically 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.10 We think, therefore, that the impairment of intracortical inhibition cannot be regarded as the marker of a specific pathophysiological mechanism, but is likely to reflect a non-specific imbalance of inhibitory and facilitatory circuits within the motor cortex.

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The authors reply:

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

The discrepancy between the two studies1,2 may not be mainly due to the different stage of the disease between the two groups of patients. Although the duration of the disease is one factor to judge the disease stage, the severity of the disease (stage of the disease) is also positively correlated with CAG repeat number.

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

We also consider that methodological differences are very important in paired magnetic stimulation. The results strongly depend on the intensities of both a conditioning and a test stimulus. Especially, the intensity of the conditioning stimulus is critical. We have no difficulty in showing normal inhibition, but have much difficulty in showing reduced or absent inhibition because of such marked dependence of the results on the intensities of stimuli. Therefore, we used an intensity of the conditioning stimulus before we confirmed inhibition in studies of patients.1 We used an intensity of 5% less than the active threshold as a conditioning stimulus, a facilitatory effect must often superimpose on the intracortical inhibition. This makes the interpretation difficult. Was the intensity of 80% of the resting threshold below the active threshold in their patients? In our experience, 80% of the resting threshold was sometimes above the active threshold. These factors must be considered in interpreting the results of paired magnetic stimulation study.

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

References:

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 (FV) during Wallenberg’s disease. This slight abnormality could be detected with their method but not with ours because their method has better sensitivity in detecting an abnormality than ours. Whichever is true, the intracortical inhibition must be normal or slightly disturbed in Huntington’s disease.

Critical closing pressure: a valid concept?

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

Firstly, the physiological meaning of both formulae of CCP presented (CCP1 and CCP2, respectively) is questionable. The implication of both presented equations is that the instantaneous value of cerebral blood flow velocity (FV(t)) at a given moment t is equal to arterial blood pressure at the given time (ABP(t)) minus CCP divided by cerebrovascular resistance (CVR):

\[ FV(t) = \frac{(ABP(t) - CCP) \times CVR}{CVR} \]  

(1)

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

\[ FV(t) = \frac{(ABP(t) - CCP) \times CVR}{CVR} \]

(2)  

F1=A1/CVR  

(3)

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

\[ CCP2=\frac{ABP(A1/F1) \times CVR}{CVR} \]

(4)

leads to

\[ CCP2=\frac{ABP(ABP-CVR1/CVR0) \times CVR}{CVR} \]

(5)

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

\[ CCP2=\frac{0.5ABP(0.5) \times CVR}{CVR} \]

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

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

Thirdly, it seems doubtful that CCP2 could be estimated using pressure and flow values from ABP ranges clearly above CCP and flow values clearly above zero flow, respectively. As long as small vessels do not collapse (ABP>CCP) it is not possible to decide whether their actual wall tension is determined more by transmural pressure or by active vasoconstriction. However, the relative contribution of both effects is critical for the limit of CCP.

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

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

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

(6)

and equation 5 to:

\[ CCP2=\frac{ABP(1-CVR1/CVR0)+CVR1}{CVR0} \]

(7)

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

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

CCP=ICP+active tension of arterial walls

Asadil proposed the mathematical formula taken for calculations:

\[ CCP1=ABP-ABPpp/FVpp+FM \]

(8)

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

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

\[ CCP2=ABP(1) \]

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 considerations of Dickl (equations 1–5) must contain an error!

First of all we cannot see how equation (1) from Diehl’s letter can be derived from any of our formulae. Everyone who has tried to plot momentary values from ABP pulse waveform against momentary values of FV waveform knows that it never plots a straight line (equation (1) implies). The “clouds” of systolic and diastolic values of ABP and FV waveforms (fig 1 in’1) 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 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 between them 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 CCP calculation”. We have not used it and have never suggested anyone could do so.

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

The final issue concerning negative flow 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
risks. How risky— we can see from Dichi’s letter. Cerebrovascular resistance certainly never increases to infinity, only after death. We fully agree with the considerations regarding equations (6) and (7). CCP can be critical closing pressure in cerebrovascular circulation. J Neurol Neurosurg Psychiatry 1999;66:606–12.


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.1 Levodopa induced dyskinesias are currently thought to share a similar pathophysiology2 but recent findings also suggest that abnormal patterns of neuronal firing in the globus pallidum internum may be as relevant.3 Data from both Parkinsonian monkeys and patients with Parkinson’s disease submitted to 2-DG uptake studies have shown increased activity in the subthalamic nucleus, which was blocked by high frequency stimulation.4 Measurement ofafferent synaptic activity by the technique of 2-deoxyglucose (2-DG) uptake showed an increment in the subthalamic nucleus, which was compatible with increased inhibition from the globus pallidum externum, particularly in the ventromedial tip of the nucleus.5 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 study6 also showed that the cortical-subthalamic nucleus connection 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.7 All this heterogeneity may have pathophysiological relevance, one aspect of which could be the findings in the patient reported by Figueiras-Mendez et al.8 However, before the findings of this case may be used to sustain a further discussion on the role of the subthalamic nucleus in the origin of levodopa induced dyskinesias, there is a crucial issue to resolve—namely, the location of the tip of the stimulation electrodes.

There are several points leading us to question the actual site of action of the electroceutical stimulation. (1) Stimulation of the subthalamic nucleus in Parkinson’s disease has been associated with the production of dyskinesias only after reduction in levodopa intake.9 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 to stimulation, due to the fact that following the thalamic nucleus from the globus pallidum internum are placed dorsocaudally to the subthalamic nucleus and could be blocked by high frequency stimulation.10 (2) When the recording electrode is placed caudally to the subthalamic nucleus in sagittal planes 11 mm or less, neuronal activity is characterised by action potentials of large amplitudes (0.5–1 mV) with 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 region of the subthalamic nucleus is different from the above but on occasions the distinction may not be easy. Accordingly, it is very important to document in more detail the findings in the case of Figueiras-Mendez et al.11 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 ent recording tracks, the evaluation of changes when further lowering the microelectrode tip from the subthalamic nucleus in the lateral region of the subthalamic nucleus in the origin of hemiballism and levodopa induced dyskinesias, there is a crucial issue to resolve—namely, the location of the tip of the stimulation electrodes.

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

Recognition of the electrical activity of the subthalamic nucleus in basal ganglia dyskinesias is based on the following 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.12 When rhythmic discharges were recorded irregular passive manipulations were performed or the patients asked to move the limbs irregularly; (d) response to tremor activation. Positive cells were so considered based on the correlation of the EMG and the accelerometer recorded simultaneously. Artificial manual stoppage 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 zona incerta and zona reticulata correlates with the circuitry of the subthalamic and zona incerta with proper characteristics; (f) a change in the background basal noise when entering the subthalamic nucleus. A higher activity is observed; (g) sensitivity is observed when the electrode penetrates the zona reticulata. A lower background noise level; (h) the activity of substantia nigra pars reticulata cells when further lowering the microelectrode. These cells discharge at high frequency at regular intervals as identified in patients and primates.13 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 dystonia 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 recognize 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. In our report, cells discharged tonically, but also fired phasically with a well-differentiated activity by a probe burst activity and identified by statistical means (autocorrelation and interval histograms).

(c) Motor responses and tremorgenic cells in line with the above mentioned criteria were found along the trajectory of the electrode. Unfortunately, this point was not mentioned in the paper. It would surely have changed the opinion of Obeso et al.

A fractionated 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 also positive to tremor. The stimulating electrode was placed in laterality 12. Two tracks were performed. In the left hemisphere, two tracks were performed. One track was performed by the poor responding activity of the cells recorded. In the other track, nine neurons were recorded in the subthalamic nucleus (always following the above mentioned criteria) with a mean of 69 Hz (range 17–98 Hz). Five cells responded to passive and/or voluntary movements. One of them was also positive to tremor. The stimulating electrode was placed in laterality 12. The effective stimulating voltage was always tested in the surgery before cementing it and, only when the symptoms are considered of unquestionable benefit it is left in the chosen place. The final position of the electrodes, assessed by ventriculography, was as follows: (a) posteroventral: 1.5 mm behind the mean point of intercommisural line, (b) height: 6.5–6.5 mm below the intercommisural line, and (c) lateral: 12 mm for the right hemisphere, and 11.5 mm for the left hemisphere.

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Nitrergic activity in acute ischaemic stroke

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

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BOOK REVIEWS


That neuroimmunology has come of age is demonstrated by the profusion of volumes published on the subject in recent years. This volume focuses on the central nervous system, and aims to satisfy the curiosity of both the clinician faced with a diagnostic problem and the ongoing studies such as the The Neurological Conditions of Isolated Demyelination, acute inflammatory demyelinating disorders examine syndromes of isolated demyelination, acute disseminated encephalomyelitis and allied conditions, and some of the syndromes of demyelination that are now accepted as part of the range of multiple sclerosis. The chapters on demyelinating disease are drawn to a close by a discussion of existing and experimental therapies for multiple sclerosis. The book continues with chapters on paraneoplastic disorders of the CNS, stiff man syndrome, neurological complications of...
connective tissue disorders, organ specific autoimmunity, sarcoidosis, and cerebral vasculitis.

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

JON SUSSMAN


As Alzheimer’s disease becomes of increasing importance to society, basic science research in this field needs to provide the building blocks for both therapeutic interventions and accurate diagnosis. This publication is a collection of papers presented at an international Alzheimer’s disease research meeting in Leipzig in 1997. This conference aimed to cover 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 fundamental research reports to reviews of the current literature. The review papers are generally excellent, concise, clear, well referenced, and illustrated—for example, there are excellent reviews of Alzheimer’s disease with vascular pathology (Pasquier et al), and Lewy body disease (McKeith et al), great updates on neuropathology (Jellinger and Bancher, Braak et al), and several worthy reviews of treatment strategies for Alzheimer’s disease including NSAIDS (Müller), antioxiants, and radical scavengers (Rosier et al). I found the review by Reisberg et al on ontogenic models in the understanding of the management of Alzheimer’s disease particularly interesting. However, the papers of original research are of more limited interest to the general reader. Although, as mentioned, the quality of illustrations is good, there is some variability in the definition of abbreviations and occasional lapses into other European languages.

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

CLARE GALTON

Alasdaire Coles


Organ transplantation, once medical exotica, is now almost routine. In the United Kingdom each year are performed cadaveric organ transplants of about 1800 kidneys (in addition to 160 live kidney donors), 700 livers, and 450 heart/lungs (UK Transplant Support Service, 1997). In basic surgical techniques were established at the beginning of the century in canine models. Transplantation of these experiments to humans awaited safe and effective immunosuppression. Until the 1960s, the only forms of immunosuppression in radiation (total body or total lymphoid) and non-selective chemical reagents (benzene and toluene). Then the antiproliferative drug 6-mercapto- penone (MPA), soon followed by a derivative, azathioprine, with improved oral bioavailability. Combined with corticosteroids, these allowed the first human solid organ transplants to be performed: in 1963 the first lung transplant in Mississipi and liver transplant in Colorado. Then in 1967 Christian Barnard captured the world’s imagination with the first heart transplant. His technique has been modified slightly since, being increasing success of organ transplantation rests mainly on improved immunosuppression with drugs that selectively suppress lymphocyte by inhibiting lymphokine generation (cyclosporin A, tacrolimus), or drug transduction (sirolimus, leflunomide), or differentiation (15-deoxyspergualin) pathways. As a result, over the last 10 years in the United Kingdom, the 1 year survival of grafts has improved from 80% to 90% (kidney), 55% to 75% (liver), and 70% to 90% (heart/lung).

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


Volume nine of the Current Issues in Neurodegenerative Disease series examines the interplay between cerebrovascular disease and dementia, particularly Alzheimer’s disease. Two hundred pages of what are essentially 20 brief review articles comprise this text, sadly without any illustrations. But the introduction to each chapter there is a certain sense of deja vu, although on the positive side each contribution is extremely well referenced.

The books is divided into five sections covering the historical concepts of vascular and Alzheimer’s dementias, the arguments for a pure vascular dementia, the role of Alzheimer’s disease in the genesis of dementia after stroke, the complications of white matter changes on neuroimaging to dementia, and finally a short section examining practical questions such as the management of stroke in patients with dementia. Although commonly recognized as they are their own right, stroke and Alzheimer’s disease do seem to cross paths more often than would be expected by chance alone, and more often than can be explained by the presence of unproved angiopathy and recurrent lobar haemorrhages. Perhaps common genetic factors are responsible and here the APOE alleles are discussed. The comprehensive section deep white matter lesions seems to explain the connection further—and convinces the reader that there is still a lot which is not well understood. It is in this section particularly that illustrations are greatly missed. Brief mention is made of other conditions which may produce white matter changes and dementia such as CADASIL, cerebral lupus, and the primary antiphospholipid syndrome.

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

PETER MARTIN


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

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

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

**DUNCAN MCLEAN**


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

Moving on from the general to the particular, the text, although expansive in parts, glosses over some important points. Examples include (a) which oral vitamin K preparations are considered safe in pregnancy (phytomenadione), (b) differential efficacy of various antiepileptic drugs in different syndromes versus side effect and teratogenicity profile, (c) more information on the limitations of available evidence to support the statement “no monotherapy human abnor- mality reported” with certain new antiepileptic drugs in pregnancy, (d) the need to consider antiepileptic drug-avoidance in pregnancy. The chapters (the dimensions would fit comfortably into the pocket of a clinical white coat, were they still to be worn) but more senior clinicians will find plenty of use for it in the clinic. It does not aim at a difficult tradition, but provides a useful list of references.

There are a few cavils. The section on treatment of anxiety is skimpy (one and a half pages) compared with say the treatment of substance misuse. Then come two weak chapters on behavioural disturbances in old age and the violent patient in the community. This last chapter will be of particular interest to community psychiatrists, a fact that I would recommend because some aspects of the practical management of violence are missing—for example, a documented risk/benefit analysis, good failsafe communication, or deciding when to detain. One of the last chapters is a very good account of the management of hyperactivity in childhood, with good practical advice on the use of methyphenidate.

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

**SIMON FLEMINGER**


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

There are a few cavils. The section on treatment of anxiety is skimpy (one and a half pages) compared with say the treatment of affective illness (22 pages) or schizophrenia (59 pages). The brevity is only partly explained by the undeveloped state of that particular area of psychopharmacology. Sections on conditions to and indications for lumbar puncture and indications for EEG seem to have been displaced from some other primer for busy junior doctors. There is no index.

These quibbles apart, prescribing guidelines can be wholeheartedly recommended.