Facial diplegia with paraesthesias: facial nerve enhancement in three dimensional MRI

Facial diplegia (bilateral facial paralysis) is a rare clinical finding that can be the presenting symptom in a wide range of diseases. It occurs in about 50% of patients with Guillain-Barré syndrome (GBS). Guillain-Barré syndrome causes regional and functional variants with unusual features. Ropper described four patients with facial diplegia and distal limb paraesthesias, and he defined them as having a rare variant form of GBS because of shared clinical, electrophysiologic, and CSF features. The anatomy and nosological position of facial diplegia presenting in this variant form is still controversial. We experienced a patient who had bilateral facial paralysis, distal limb paraesthesias, and diminished reflexes whose contrast-enhanced three dimensional MRI (3-D MRI) showed enhancing lesions in the bilateral facial nerves.

A 27 year old woman had nasal discharge and coughing. One week later she noticed paraesthesias in her fingers and toes. Nine days after the onset of her neurological symptoms, she developed bilateral facial weakness. On admission (day 12) she showed moderate, bilateral facial paralysis that caused her difficulty in moving her forehead, in approximating her eyelids, and in lifting the corners of her mouth and her nasolabial folds. The other cranial nerves were normal. A motor examination showed normal strength in her limbs. Superficial and deep senses were normal even though she had distal limb paraesthesias. Deep tendon reflexes were absent in all her limbs and her plantar responses were flexor type. Cerebellar ataxia and autonomic nervous dysfunction were excluded. Chest radiography was normal. Laboratory studies of the identifiable causes of facial diplegia (sarcoidosis, Lyme disease, syphilis, infectious mononucleosis, herpes simplex virus, diabetes mellitus, and connective tissue disease) were all negative. On day 12, the CSF examination detected mild increases in protein concentration (57 mg/dl) without pleocytosis. The blink reflex was elicited and both the R1 and R2 components were reduced, but their latencies were not prolonged on day 15. Motor and sensory nerve conduction velocities, and median and tibial nerve frespawns were all normal on day 18. Auditory brainstem responses were normal. On Day 19, when her facial diplegia was moderate, conventional brain MRI detected no abnormality. A contrast-enhanced 3-D MRI, which was obtained by spoiled gradient recalled acquisition in the steady-state sequence using a 1.5 tesla system after injection of gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA), was performed. The intracranial segments of the bilateral facial nerves were remarkably enhanced by Gd-DTPA (figure). On Day 45, when her symptoms were no longer present, there were no abnormal enhancements of her facial nerves.

After showing symptoms of upper respiratory infection, the patient experienced the acute onset of facial diplegia, distal limb paraesthesias, and areflexia but no other neurological deficits. The CSF examination showed albuminocytological dissociation, and clinical and laboratory examinations excluded the possibility of viral or bacterial infection, Lyme disease, tumour, sarcoidosis, cerebrovascular disease, diabetes mellitus, bilateral Bell’s palsy, and congenital and familial disorders. The patient’s illness followed a monophasic course. We therefore diagnosed this case as having “facial diplegia with paraesthesias”, which should be included for the differential diagnosis whenever sudden bilateral facial paresis occurs. Routine brain MRI showed no abnormalities, whereas contrast-enhanced 3-D MRI showed Gd enhancement of the bilateral facial nerves. The MRI findings indicate the involvement of the peripheral facial nerves in our patient. Fulbright et al reported an additional case of GBS with multiple cranial nerve enhancements seen on Gd enhanced MRI. The mechanism of abnormal enhancement of the cranial nerves in the patients with GBS is not entirely understood; however, it is widely regarded as disruption of the blood nerve barrier by the inflammatory infiltrate. Ramsey et al evaluated the MRI findings obtained with Gd contrast enhancement in five patients who had GBS and bilateral facial paralysis: GBS (n=1), herpes simplex polyneuritis (n=1), meningeval lymphoma (n=1), and bilateral Bell’s palsy (n=2). Gd enhanced MRI has been shown to be the procedure of choice for demonstrating inflammatory lesions of the facial nerves. Nagaoka et al showed oculomotor nerve enhancement on 3-D MRI in Fisher’s syndrome, the best known variant of GBS. Ours is the first report of facial nerve enhancement in “facial diplegia with paraesthesias”. These findings suggest that 3-D MRI with Gd-DTPA can be used to identify inflammatory conditions that produce peripheral lesion of the cranial nerves in GBS variants.

Restless legs syndrome associated with spinal cord lesions

Restless legs syndrome may be either a primary or a secondary disorder. The primary form of the syndrome is often familial whereas the secondary form is mainly associated with pregnancy. Almost all patients with restless legs syndrome show periodic leg movements during sleep. The pathogenesis of both restless legs syndrome and periodic leg movements is still speculative. Yokota et al reported an association of periodic leg movements with spinal cord lesions. However, none of these patients had the typical clinical features of restless legs syndrome. Restless legs syndrome associated with myelopathy is documented in one patient with a Borrelia induced myelitis. We report three patients who developed a restless legs syndrome in close temporal association with spinal cord lesions.

Case 1 was a 35 year old woman who presented with a 3 week history of painless restlessness of her left lower leg that occurred only at rest, particularly in the evening and at night. The restlessness was partially relieved by walking. With the onset of these symptoms, the patient had noticed a numbness of her left hemibody below the breast. Nine months previously, a numbness of the foreleg had subsided spontaneously within 1 week. On examination, the patient had decreased senses for touch, pain, and temperature over the left hemibody below the T6 dermatome. Examination of the legs revealed normal cell count, normal protein content, increased CNS synthesis of IgG, and positive oligoclonal bands. In MRI studies of the spinal cord, no abnormality was documented. MRI was not performed. Transcranial magnetic stimulation showed a slightly prolonged central conduction time of motor evoked potentials recorded over the left abductor hallucis muscle. Otherwise, multimodality evoked potentials were normal. A myelitis due to multiple sclerosis accompanied by a symptomatic unilateral restless legs syndrome was diagnosed. The patient was treated with 500 mg prednisolone intravenously over 5 days without any clinical effect. However, a single dose of 100 mg levodopa plus benserazide led to a dramatic improvement of the restless legs syndrome. The levodopa treatment was continued and resulted in complete relief.

Case 2 was a 49 year old man who had a traumatic atlantoaxial dislocation that necessitated operative stabilization of the cervical spine. Preoperative MRI studies had shown a compression of the medulla and the cervical cord. When we saw the patient 3 years later, he complained of a sensation of cold, pain, and restlessness in both lower legs that was present only at rest, particularly in the

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evening, and was relieved by walking around and rubbing the legs with cold water. The onset of these symptoms was only a few weeks after the accident. Clinical examination disclosed a mild dysarthrophy and atrophic pareses of the left sternomastoid and the left shoulder muscle. Tendon reflexes were hyperactive and plantar responses were extensor bilaterally. The patient’s gait was spastic, but he was able to walk unassisted. In both legs, pain and temperature sensation were markedly reduced. The diagnosis of a restless legs syndrome secondary to a traumatic lesion of the medulla and the cervical cord was made. Treatment with 100 mg levodopa plus benserazide and 100 mg tramadol resulted in a satisfactory relief of the restless legs syndrome.

Case 3 was a 65 year old man who developed slowly progressive spastic tetraparesis and ascending sensory disturbances in both legs. An MRI study showed a cervical spondylotic myelopathy at the level C3-C6 and the patient underwent spinal cord decompression. Five years later, he was referred to our hospital because of an intense restlessness in the feet and calves. The restlessness occurred when sitting and lying for more than 20 minutes. It was pronounced at night and improved when he was walking around. The symptoms started simultaneously with the motor and sensory disturbances due to the cervical spondylotic myelopathy and did not improve postoperatively. On examination, the patient was mildly impaired in carrying out fine motor tasks and his gait was moderately spastic. He had reduced touch and vibration senses in both upper limbs. A restless legs syndrome due to a cervical spondylotic myelopathy was diagnosed. Treatment with pergolide resulted in an excellent control of the restless legs syndrome.

Our patients meet the criteria for the diagnosis of restless legs syndrome.1 Over a follow up period of at least 6 months, restless legs syndrome symptoms were sufficiently relieved by dopaminergic treatment. The association of myelopathy and restless legs syndrome may be merely coincidental. However, the close temporal relation between the onset of myelopathy and restless legs syndrome strongly suggests that restless legs syndrome was secondary to the spinal cord lesion.

In conclusion, our report suggests that restless legs syndrome may occur secondary to spinal cord lesions due to different causative diseases including multiple sclerosis, spinal cord injury, and cervical spondylotic myelopathy. Similar to idiopathic restless legs syndrome and other secondary forms, restless legs syndrome due to myelopathy may respond well to dopaminergic drugs.

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Coma in thrombotic thrombocytopenic purpura

Patients with thrombotic thrombocytopenic purpura (TTP) can present with devastating neurological abnormalities.1 Mortality may be as high as 95%, but current treatment has reduced this to about 10% and early treatment improves the rate of recovery.2 We describe two patients who presented with predominantly neurological symptoms and signs who, because of a delay in making a diagnosis of TTP, were referred for treatment at a late stage. Both patients were reviewed by neurologists and haematologists in our hospital, and it was considered that the diagnosis was poor. The first case was a 49 year old woman with a longstanding diagnosis of schizophrenia and a previous left sided cerebrovascular accident. She was admitted to her local hospital with a 3 day history of drowsiness, confusion, epistaxes, and spontaneous bruising, having been noted to be increasingly agitated and disoriented over the preceding 6 weeks. Her only medication was trifluoperazine and paroxetine. The second case was a 58 year old man, previously fit and well, who was transferred to our hospital with a 3 week history of confusion, drowsiness, jaundice, and right upper quadrant pain. He was taking no medication. The initial findings in both patients are summarised in the table. In both a diagnosis of TTP was made, although this was not confirmed for the second patient until 7 weeks after admission. The diagnosis was made following the development of neurological symptoms and signs.4

Treatment was started in both cases with five cycles of plasma exchange using 3 l cryodepleted fresh frozen plasma, and in the first patient this was followed by a course of oral prednisolone and azathioprine. Both made an excellent recovery, with an improvement in consciousness and a rise in platelet count, disappearance of red cell fragments, a fall in LDH and bilirubin concentrations, and normalisation of renal function. The first patient was self ventilating with no neurological deficit at time of transfer back to the referring hospital. The second patient had a Glasgow coma score of 15 by the fifth day of treatment, the only focal neurological being a bilateral internuclear ophthalmoplegia (INO). Three months later the ophthalmoplegia had resolved and the patient was self caring with minimal disability. Both patients were extensively investigated to look for an underlying cause for TTP, but none was found.

Thrombotic thrombocytopenic purpura is a syndrome comprising a pentad of features—fever, thrombocytopenia, microangiopathic haemolytic anaemia, neurological abnormalities, and renal dysfunction. Not all five features are required to make the diagnosis of TTP.

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**Table:** Summary of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Platelet count (x10^9)</th>
<th>Peripheral blood film</th>
<th>Clotting screen+fibrogen</th>
<th>Bilirubin (µmol/l)</th>
<th>Lactate dehydrogenase (U/l)</th>
<th>Creatinine (µmol/l)</th>
<th>Glasgow coma score</th>
<th>Neurological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>49</td>
<td>F</td>
<td>19</td>
<td>RBC fragments +++</td>
<td>Normal</td>
<td>67</td>
<td>931</td>
<td>121</td>
<td>3/5</td>
<td>Pupils equal and reactive, cornal reflexes intact, bilateral jaw jerk, brisk, gag absent; no motor response to painful stimuli; reflexes absent; upgazing plantar responses Normal</td>
</tr>
<tr>
<td>Patient 2</td>
<td>58</td>
<td>M</td>
<td>17</td>
<td>RBC fragments +++</td>
<td>Normal</td>
<td>49</td>
<td>131</td>
<td>3/15</td>
<td>Midposition, non-reactive pupils, consensual gaze in all directions; extension of all four limbs to painful stimuli; plantars equivocal</td>
<td></td>
</tr>
</tbody>
</table>

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**Notes:**

diagnosis—often fewer are present—and there is no pathognomonic test, so diagnosis may be difficult. It is often considered along with haemolytic uraemic syndrome (HUS) to form part of a range of diseases called the thrombotic microangiopathies. In these disorders, intravascular platelet aggregation (there is minimal fibrin deposition) leads to obstruction of arterioles and capillaries, causing local ischaemia. Thus TTP is seen when the cerebral microcirculation is affected, and HUS when the renal microcirculation is affected. An episode of TTP may present as a one off illness, may be recurring, or may arise in association with drugs, neoplasia, pregnancy, or HIV infection.

Thrombotic thrombocytopenic purpura presents with neurological manifestations in over 50% of episodes, with headache, confusion, and somnolence being most common, leading to focal neurological deficit, convulsions, and eventually coma and death. These clinical features are often fleeting and fluctuating and several important points regarding investigation should be made. Firstly, brain CT may be normal or may show multiple hypodense areas indicative of generalised cerebral oedema. Secondly, brain MRI may also be normal, although it is likely to show multiple areas of high intensity on T2 weighted images. Coma has been shown to be a bad prognostic indicator. Of importance is the finding that despite the presence of substantial cerebral oedema, normal findings on brain CT strongly suggest the potential for full clinical recovery. Plasma pheresis is now the treatment of choice: plasma infusion alone should not be considered an acceptable alternative but as a short term measure only. Fresh frozen plasma is the usual replacement fluid, although it remains to be determined whether cryoprophylactant or solvent/detergent fresh frozen plasma is more effective. These plasmas lack von Willebrand factor, and since ultralarge von Willebrand factor multimers are postulated to play a role in the pathogenesis of the disease, Platelet transfusions should be avoided (unless there is life threatening bleeding) as they may worsen the condition. These two cases illustrate that patients with TTP may present with the intensive care unit with profound coma, such that many clinicians would consider the prognosis so poor that further active management would be inappropriate. In addition, the cases show that patients can survive and even make a full recovery despite a delay in diagnosis and appropriate treatment.

**Anaphylactoid reaction to methyl prednisolone developing after starting treatment with interferon β-1b**

Courses of intravenous methyl prednisolone are a routine form of therapy, for disabling relapses in relapsing-remitting multiple sclerosis. The Interferon β-1b Multiple Sclerosis Study Group’s research published in 1993 showed that interferon β-1b reduces the frequency of relapses in patients with multiple sclerosis. We present the case of a 35 year old man with multiple sclerosis who became allergic to intravenous methyl prednisolone after the initiation of treatment with interferon β-1b and discusses what part the drug could have played in this.

A 35 year old man with asthma presented early in 1994 with “dizziness”, double vision, and paraesthesia in the right leg extending into the trunk. He had no history of migraines and no prior history of a similar urticarial rash. Again treatment was successful and the rash resolved. On examination of the brain with magnetic resonance imaging there were multiple periventricular high density lesions with a similar lesion identified on imaging of the cervical cord, all consistent with demyelination. A 3 day course of intravenous methyl prednisolone was associated with improvement in his initial symptoms. Four months later he presented with a Vth nerve palsy which again responded to a 3 day course of intravenous methyl prednisolone. Between September 1995 and February 1996 he had a further four uneventful 3 day courses of intravenous methyl prednisolone for various symptoms related to his multiple sclerosis. In March 1996 he was started on interferon β-1b (8 MIU subcutaneously on alternate days).

In June 1996 he was admitted with pyramidal weakness of the left limbs, altered sensation in the left leg and urgency of micturition. Soon after starting his first dose of intravenous methyl prednisolone he felt a “jump” in his throat, developed a urticarial rash on his limbs and trunk and began wheezing audibly. Intramuscular chlorpheniramine was ineffective. Treatment was stopped and his peak expiratory flow rate (PEFR) measured as 485 l/min. Chlorpheniramine (10 mg) was given intravenously and after 5 minutes his PEFR had returned to 75% of his normal PEFR at 550 l/min. Further methyl prednisolone was not given on this occasion.

In August 1996 he was admitted with symptoms similar to those at his admission in June 1996. Ten minutes after starting his first dose of intravenous methyl prednisolone his chest felt tight and he started developing a similar urticarial rash. Again treatment was stopped. Fifteen minutes later the rash had worsened and he felt swelling in his mouth. His symptoms settled after 10 mg intravenous chlorpheniramine. Further methyl prednisolone was not given. After this episode he chose to stop interferon β-1b.

In September 1996 he developed wheeze and a rash after the first dose in a course of intravenous methyl prednisolone. Subsequent doses in that course were preceded by chlorpheniramine. In November 1996 he developed nasal congestion and a rash after 500 mg methyl prednisolone. Again subsequent doses were preceded by a dose of chlorpheniramine.

Allergic reaction to steroids is rare and anaphylactoid reaction to methyl prednisolone is rarer still with only three reports in the literature. One of these reactions occurred in the course of treatment for multiple sclerosis. The allergic reactions are more likely to be to the carrier than to the steroid itself. Pathology in multiple sclerosis is thought to be due to a delayed type hypersensitivity reaction. The mechanism of action of interferon β-1b is unknown, although several mechanisms are postulated. There is evidence that, among its many effects on the immune system, interferon β can increase interleukin-2, and that interleukin-2 can stimulate a Th2 response (found in allergic type responses). These effects would explain the sequence of events in this man. However, evidence suggests that interferon β is more likely to suppress both Th1 and Th2 responses. It remains uncertain whether the sequence of events here is due to an effect of interferon β-1b or to an unrelated mechanism. However, clinicians should be aware that the complexity of the effects of interferon β-1b on the immune system may lead to unexpected clinical outcomes.

**References**


Poststreptococcal neuropathy

Streptococcal infection can lead to a wide range of sequelae. Peripheral nervous system injury is not well known as one of its possible complications. We report a case with a typical history for a poststreptococcal vasculitis causing an axonal neuropathy of the right common peroneal nerve.
A 17 year old girl was referred by her general practitioner due to the sudden onset of numbness on the dorsum of her right foot associated with stamping her foot on walking. She had been well until 6 weeks previously when she developed tinitus for which she received a 1 week course of oral penicillin V. She was also taking minocycline for mild acne. As her throat recovered she developed symmetrical distal polyarthralgias and plantar sweats which persisted as the numbness developed. There was no history of trauma or compression of the common peroneal nerve at the neck of the fibula.

On examination she had a right foot drop with weakness of ankle dorsiflexion (Medical Research Council grade 3/5). There was sensory loss in the distribution of the common peroneal nerve. She was otherwise neurologically intact with normal reflexes. There were no skin lesions and her joints were quiescent.

She had an erythrocyte sedimentation rate of 87 mm/h, a C reactive protein concentration of 112 mg/l and an anti-streptolysin-O titre (ASOT) of 1600 units/ml. Autoimmune screen, antineutrophil antibodies, and cryoglobulins were all negative apart from an atypical perinuclear antineutrophil cytoplasmatic autoantibody (p-ANCA) IgG titre of 160. Renal function was normal and there were no casts on urine microscopy.

Nerve conduction studies showed uniform reduction of compound motor action potential amplitude from all sites of stimulation of the right peroneal nerve with mild slowing of conduction velocity. Sensory studies disclosed an absent response from the right superficial peroneal nerve (table). F wave late responses were normal in the right tibial (with true H response) and left peroneal nerves, but delayed and inconsistent in the right peroneal nerve. Needle EMG was normal in the right tibialis posterior muscle providing evidence against the lesion being at the L5 root level. There were, however, only two units recruited from the right tibialis anterior with small responses of long duration and no spontaneous activity. The tests confirmed a mainly axonal neuropathy of the right common peroneal nerve with no evidence of entrapment.

Because of its link with autoimmune disease the minocycline was stopped and she developed a vasculitic skin rash over the dorsum of both feet. A biopsy showed deposits of C3 and fibrin in the walls of some superficial dermal vessels consistent with a vasculitis. A 3 day course of intravenous methylprednisolone was followed by azathioprine and prednisolone. The decline in her ASOT and inflammatory markers mirrored the improvement in her systemic symptoms although on stopping immunosuppression after a 2 month course she developed erythema nodosum necessitating further steroid therapy. Her foot drop has improved although she has persistent sensory loss.

In conclusion this is a 17 year old girl with a typical poststreptococcal syndrome associated with constitutional symptoms, arthralgias, microscopic polyangiitis, and later erythema nodosum. As part of her illness she developed a mononeuropathy with no evidence to suggest a specific antineuronal process and likely to be due to a nercotising vasculitis. It is unlikely that the streptococcal infection has unmasked a connective tissue disorder due to the negative autoimmune screen apart from the atypical perinuclear antineutrophil cytoplasmatic autoantibody (p-ANCA) IgG titre of 160. Renal function was normal and there were no casts on urine microscopy.

We recently encountered a patient with sensory loss of the spinothalamic type involving only the contralateral leg and lower trunk from vertebral artery dissection. The sensory level in our patient with facial sparing differs from those in the literature; it suggests a thoracic hemisclerotic lesion and is false localisation.

A 44 year old, right handed man with no relevant history presented with sudden onset of vertigo and left eye pain. There was no history of trauma or neck manipulation. However, the patient had had a dental abscess involving the lower incisors requiring draining 4 weeks previously. He has a 30 pack-year history of smoking. Vertigo developed while he was changing his car tyre. He noted that the vertigo was worse when he sat down and put his head between his knees. The vertigo lasted 15 minutes and was associated with profuse sweating in the upper half of his body. There was no nausea or vomiting. This recurred twice that day each time lasting 15 minutes.

Examination disclosed normal visual acuity and fundoscopy. There was scleral injection in the left eye. The left pupil was 4 mm compared with 5 mm on the right. Both reacted briskly to light. There was counterclockwise rotary nystagmus in the primary position. The eye movements were normal. Corneal reflex was intact, and there was no sensation to the upper and lower face. The other cranial nerves were normal. The gag reflex was brisk. There was no cranial bruit, Töne, power, and reflexes were normal. The sensory examination was normal in all modalities. There was no upper limb ataxia. He tilted to the left on sitting and on standing he fell to the left. The next day he noted loss of pinprick and appreciation of temperature on the right leg and trunk with a sensory level at T9 with preservation of touch, vibration, and joint position sense in all limbs (figure).

Brain MRI showed a small infarct in the lateral medulla and left cerebellum in the
Sudden unexpected death: a rare event in a large community based prospective cohort with newly diagnosed epilepsy and high remission rates

It is now accepted that mortality in epilepsy is significantly increased, with standard mortality ratios raised twofold to threefold. Early deaths are usually attributable to the underlying cause of epilepsy and mortality in chronic cases is commonly due to the epilepsy itself.1 Of the deaths that are directly related to epilepsy, the commonest category is sudden unexpected death in epilepsy (SUDEP). This is widely defined as a sudden unexpected, non-traumatic and non-drowning death in a person with epilepsy with or without evidence of a seizure and excluding documented status epilepticus in which postmortem examination does not disclose a cause of death. Less common causes are status epilepticus, accidents due to seizures, drowning, and aspiration of vomitus in patients with epilepsy.2 The mortality of epilepsy is not precisely known. Studies have varied in their methodology and study populations have ranged from those in death certificate and coroners’ registers (more community based) to epilepsy surgery cohorts and institutionalised patients (patients with chronic epilepsy).3 Figures derived from community based prospective studies indicate numbers of SUDEP deaths of up to 1:1100.4 Patients with chronic epilepsy seem to have a much higher incidence of SUDEP and a tertiary clinic based population with chronic epilepsy in the United Kingdom had an estimated incidence of 1:200 patients.5 This is in some contrast with the two SUDEP deaths in 5000 patient-years reported by the MRC Anti-Epileptic Withdrawal Study Group for patients in remission from epilepsy.6

We report the first sudden unexpected death in epilepsy in the NGPSE. A 42 year old man known to have poorly controlled idiopathic generalised epilepsy treated with phenytoin and sodium valproate, was found dead in bed, having been well in the hours and days preceding death. He was known to misuse alcohol and was questionably compliant with medication, both factors thought to increase the risk of sudden death. A necropsy did not disclose any relevant pathology—consistent with the definition of SUDEP.

Mortality has been studied in detail in this large cohort7 and it was only in the 13th year of follow up (8000 patient-years) that the first SUDEP was reported. This could falsely give the impression that SUDEP is a rare occurrence and it must be borne in mind that in large community based cohorts such as the NGPSE, most patients enter remission from seizures and it is the patients who continue to have epilepsy that are most at risk from sudden death. Indeed in this cohort, the number of patients who still have active epilepsy, based on standardised mortality ratio among patients with definite epilepsy in this cohort was 3.0 (95% confidence interval (CI) 2.5–3.7).8

The true incidence of SUDEP is not precisely known. Studies have varied in their methodology and study populations have ranged from those in death certificate and coroners’ registers (more community based) to epilepsy surgery cohorts and institutionalised patients (patients with chronic epilepsy).3

(A) Drawing of sensory deficit; (B) MRI showing clot in the left vertebral artery and infarcts in the lateral medulla and cerebellum (arrow), (C) arrowhead pointing at the occlusion of the left vertebral artery.


2 Masamoto S, Okada B, Imai T, et al. A sensory level to the trunk may point to a lateral brainstem lesion in the presence of other features suggesting brainstem disease. In our patient these signs were transient and sensory loss predominated. This new pattern of sensory loss should be recognised as symptomatic of lateral medullary infarction in addition to other sensory variants.9

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Financial support and sources of funding for the NIGHE audit team would be expected. The Institute of Neurology and the National Hospital for Neurology and Neurosurgery, Brain Research Trust, and the National Society for Epilepsy.

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**CORRESPONDENCE**

**MRI in vertebral artery dissection**

In a recent report, Auer et al described the clinical and imaging findings in 19 cases of extracranial vertebral artery dissection retrospectively.1 We make the following comments.

Firstly, the authors described the “sensitivity” and “specificity” of digital subtraction angiography (DSA), magnetic resonance imaging/angiography (MRA/A), and duplex sonography for diagnosing extracranial vertebral artery dissection.1 These figures were based on the percentage of probable and definite features among the 19 patients. Nevertheless, sensitivity of a test is the number of cases with true positive results divided by the total number of positive results (including both true and false positives), and specificity is the number of cases with true negative results over the sum of true and false negatives. The authors misquoted the terms “sensitivity” and “specificity” in their report, as the diagnostic criteria of the various tests have not been applied to a control group to disclose the false positive cases and true negative cases. Secondly, the criteria for case inclusion were not defined. Apparently, extracranial vertebral artery dissection was diagnosed by either radiological features on MRA/A (which may be “pathognomonic” or “suggestive”) in the appropriate clinical context or confirmatory radiological features on DSA (which may be “specific” or “indirect”). The accuracy and usefulness of DSA, MRA/A, and duplex sonography cannot be compared directly, as no single “gold standard” diagnostic method was used and because results of the present study simply reflected the proportion of cases diagnosed by the authors.

Dissection of neck arteries was thought to be an uncommon cause of ischaemic stroke. The true incidence of this condition remains unknown as angiography is not performed in every patient during the acute or subacute phase. Younger patients are more likely to undergo early angiography when there is a history of recent neck trauma or pain, or when no other causes of stroke are apparent. This selection bias may underestimate the number of cases.
Clinical usefulness of MRI in multisystem atrophy.

Schrag et al suggest that certain putaminal and infratentorial changes on MRI are useful in distinguishing between patients with multisystem atrophy (MSA) and patients with idiopathic Parkinson’s disease.¹ The specificity and positive predictive value of these changes were both about 90%. However, whether these changes will be useful in clinical practice or epidemiological research is unclear for several reasons.

The number of patients included was small and so the confidence intervals were wide. For example, the specificity of the MRI changes for MSA could be as low as 80%. Moreover, only patients with clinically probable MSA were included. In this group of patients the clinical diagnosis alone had positive predictive value as high as that of MRI and so there would seem to be little added value of MRI (14/15 (93%) patients with probable MSA had the diagnosis confirmed by MRI). A more relevant question is whether the MRI changes are equally specific in those with possible MSA in whom the clinical diagnosis is much less certain. Indeed it is also unclear from this study whether the MRI changes specific to MSA as patients with other conditions that enter into the differential diagnosis were not included. It may therefore be more correct to state that the MRI changes are helpful in excluding Parkinson’s disease rather than in confirming MSA.

Finally, the positive predictive value of MRI quoted in this study is likely to be an overestimate compared with its routine use in most movement disorders. Schrag et al included a very high proportion of patients with MSA (nearly 50%) compared with Parkinson’s disease. As the positive predictive value is directly related to the prevalence of the disease in a given population, this resulted in a high positive predictive value. In a typical movement disorder clinic, fewer than 10% of patients will have MSA, in which case, even if the specificity of MRI is 90%, the positive predictive value would only be about 50%—that is, only half of those with the MRI changes would turn out to have the disease.

It is, therefore, too early to include specific MRI changes as part of the diagnostic criteria for MSA.

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Auer and Felber reply:
Cheung et al state in their comment, that dissections of the neck arteries are an underestimated cause of stroke, because angiography is not performed in every patient during the acute and subacute phase. This bias is even more important in the case of vertebral artery dissection if the initial symptoms are non-specific. Non-invasive diagnostic methods are likely to be performed earlier in these patients and this was our motivation to report on the neuroradiological features of vertebral artery dissection.

The diagnosis of vertebral artery dissection is often based on the consensus of clinical and neuroradiological features. We agree with Cheung that there is no single “gold standard” test for a dissection exists. Imaging procedures more often show indirect signs which have to be interpreted in the appropriate clinical context. Therefore, the “inclusion criteria” we used for this retrospective analysis was the clinical and neuroradiological consensus on the diagnosis of vertebral artery dissection.¹ The sensitivity of DSA, ultrasound, and MRI/angiography was useful in the exclusion of other vascular causes and of relevant lesions in the extracranial vertebral arteries. There were no false negative and the contralateral nor-
mal vertebral arteries, there were no false positive findings. The term specificity could have been misleading, because it did not refer to the overall specificity of a test but to the frequency of findings that reached a level of specificity sufficient to establish the diagnosis of vertebral artery dissection.¹

Further prospective studies on the sensitivity and specificity of magnetic resonance angiography and magnetic resonance imaging for the diagnosis of vertebral artery dissections are certainly necessary, but our retrospective evaluation already showed that MRI and MR angiography will have a major contribution in future. As a non-invasive means, magnetic resonance can be employed without risk in patients with non-specific symptoms and may provide specific findings that are not accessible with other methods. This will lead to a better estimation of the true incidence of dissecti-
ons and will improve the early diagnosis and management of dissections in individual patients.

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Schrag and Quinn reply:
Counsell and Hughes raise several potential drawbacks to our study that we willingly acknowledge. Firstly, that the number of patients included was small (about 45 in each group); secondly, that the 1:1 proportion of patients with Parkinson’s disease and those with multiple system atrophy (MSA) atrophy is unrepresentative of the real life situation in which the ratio is >10:1. A more ideal study might include 100 patients with MSA (to help counter the criticism of small numbers) and more than 1000 patients with Parkinson’s disease, but would be impractical, particularly for the Parkinson’s disease group. In our study, who, unlike patients with atypical disease, are not usually subjected to MRI. We agree that, as clearly stated in the abstract, our study was restricted to a comparison between multisystem atrophy, Parkinson’s disease, and controls, and are currently conducting a further study additionally including patients with other degenerative syndromes. Since the completion of the report, patients with Machado-Joseph disease were included with similar infratentorial abnormalities. We also agree that in the diagnosis of clinically probable MSA, there is little added value of MRI; involvement of the cerebellum and its pathways is usually already clinically evident before its demonstration by MRI or CT,¹ and even in cases without cerebellar involvement the diagnosis is still a clinical one. Moreover, as we emphasised, a minority of patients with probable multisystem atrophy may not have MRI. Therefore, unlike others,¹ we have never proposed MRI changes as part of the diagnostic criteria for multisystem atrophy. As discussed, the sensitivity of the method may be lower early, and higher late in the disease. Hence, for the purpose of validation of a proposed diagnostic aid imaging findings need to be related to a clinically probable diagnosis rather than a pathological one. The “gold standard” is definite, pathologically confirmed disease, but this was achieved in only one patient in our series. In conclusion, we nevertheless think that our, admittedly imperfect, blinded MRI study (the first conducted in MSA) has helped to determine the prevalence of certain MRI abnormalities in patients with clinically probable MSA in comparison to patients with Parkinson’s disease and controls. It has also, perhaps more importantly, revealed the limitations of MRI in this context. However, expert clinical evaluation remains the cornerstone of the diagnosis in life, and it is also more cost effective than resorting to expensive imaging techniques.

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A dubious therapy for patients with multiple sclerosis.

Plohm et al investigated the effects of computer training of attentional deficits in
patients with multiple sclerosis. They conclude that “significant improvements of performance could almost exclusively be achieved by the specific training programmes”. The validity of this conclusion is called into question by severe methodological shortcomings of their study.

Before training, three baseline measurements of attentional functions were administered with 3 week intervals. For evaluation of training effects the median value of the three baseline measurements was compared with the values obtained after training. This statistical approach manifests a curious misunderstanding of the purpose of repeated baseline measurements. They serve to determine a baseline measurement, the median is lower than the third measurement after which training began. This difference infers apparent improvement in the first training period. It may signify specific training effects if the training has had a steeper baseline than the control group. A possible reason for different baselines are different severities of initial impairment. We (Motz, Grömminger, Göttert, Goldenberg, unpublished data) have administered the PASAT, another test of attentional capacities, four times with weekly intervals to 30 patients with chronic brain damage from different aetologies. During intervals these patients did not receive any training of attentional functions. Thus, the repeated measurements determined a baseline without therapy. None the less, performance on PASAT improved from test to test. There was a negative correlation between performance and improvement. Patients with poor initial performance improved more than those with better performance.

The allocation of patients to treatment groups in the study of Plohmann et al was not randomised. Patients were trained in those two functions that were affected most, and group comparisons were made between patients who had been trained in a function and those who were not. Thus the training group tended to start from a lower level of performance than the control group. Figures 2 and 3 of their paper illustrate this effect impressively. If, as suggested by our results with the PASAT, initial level of impairment has a systematic influence on improvement independently of any therapy, the alleged specific training effect may be accounted for by the differences in initial level of impairment. For this reason we reanalysed our data. For each training group we built subgroups of patients according to their initial capability (low, medium, high) and printed the course of performance during the baseline measurement (T1-T3). Our results do not confirm Goldenberg’s assumption that initial level of performance has a systematic or inverse influence on improvement.

Nevertheless, as already stated in our original paper, due to the small sample size of our study the results do not allow a definite assessment of the training and its effects in patients with multiple sclerosis; but they provide enough evidence to encourage further studies in a larger population of patients. Thus, we have started a prospective multicentre study in comparison with three Swiss neurological rehabilitation centres to further assess and possibly improve this kind computer assisted retraining of attentional functions.

The unpublished additional data mentioned in our letter have been submitted with this letter and are available on request (tables 1a-1c, figures 1 and 2).

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Neurology and the gastrointestinal system

Neurology and the gastrointestinal system, or an analysis of the “brain-gut” axis would be incomplete without allusion to the neuroendocrine system, and its mediation, via somatostatin, in the regulation of splanchnic blood flow and gastric acid secretion. These actions could account for the established haemostatic action of somatostatin in oesophageal variceal bleeding, and for the perception, derived from meta-analysis, that similar benefits might occur in non-variceal upper gastrointestinal haemorrhage. On the basis of the involvement of somatostatin in the regulation of gastric blood flow and acid secretion, it seems reasonable to attribute gastric erosive bleeding, so-called Cushing’s ulcers, which occur in CNS disorders, to derangements in neuroendocrine pathways.

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Letters, Correspondence, Book reviews

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“About all we really understand about neurological disease we have learned from pathological studies.”

Self evidently not a perfect truth, but it is a fair approximation, particularly if “understand” is properly weighted. Take multiple sclerosis as a random example. We have been taught a great deal about the course and dynamics of the disease—for example, by new imaging techniques, but MRI has come closest to contributing to our understanding of the disorder when married to pathological studies, or when used as a surrogate marker of pathology. The huge power of the new genetics has now set its sights on multiple sclerosis, and although proceeding apace and well in to the genome screen approach, it too has yet to contribute major insights to our understanding of multiple sclerosis. Animal models, even the aged EAE, can only offer suggestions which live or die according to correlative studies of multiple sclerosis tissue or patients. And my own area of interest, the cell biology of oligodendrocytes studied (mostly) by cell culture, is no better or worse than these other tools: it can make suggestions which must be tested by direct examination of tissue—by pathology.

It follows that good neurology must depend on a decent grounding in pathology, and a neurological training which fails to include pathology is emphatically pathologic is a poor and incomplete one. Calman’s prescription for postgraduate education presents an opportunity formally to ensure that training schemes do not permit the possibility of such deficiency. So what would the sixth edition of *Greenfield’s Neuropathology* feature on an idealised neurological curricular reading list? It could not fail to.

To continue with the above example, the account of demyelinating disease—and with what better subject to start? Considering Greenfield’s own contributions to the pathology of multiple sclerosis, the most conspicuous at present is his definitive study of axon loss in multiple sclerosis, which surely is one of the finest wheels to be reinvented. This must be as good an account as any available. If it is (notwithstanding the book’s two volumes and 2200+ pages), not overly long—86 pages, but strikingly well structured, generously (and often beautifully) illustrated with 95 figures, the great majority photomicrographs and many in colour, and closely and carefully argued, with over 500 references. Prineas and McDonald have combined and distilled their unique and enormous experience to provide a scholarly, authoritative, and yet wholly readable review of multiple sclerosis and the associated demyelinating diseases, a benchmark account against which current and future efforts must be measured.

How to move on, to provide anything remotely resembling a useful review of the remaining 25 chapters? Several merit particular attention. “Diseases” (DeArmond and Prusiner) and “tumours of the nervous system” (Lantos, Vandenberg, and Kleihard) are both as new to Greenfield’s book. Both represent topics whose biology and pathology have changed at a breathtaking pace over the past five years, a sure challenge to any textbook harbouring ambitions of definitive. Typically, both rise to the call with apparent ease. The chapter on prion disease is only 35 pages long, but this is nevertheless a comprehensive and fine account of an extraordinary area of the human neurology and neuropathology. There are excellent descriptions not only of conventional dementing prionopa-thies, but also of rarer, more recently recognised entities such as fatal familial insomnia. The disease in which reverses and molecular dissection of the disease are amply covered, and space is even found for speculation concerning the possible involvement of prions, in yet another evasive and tantalising disease, inclusion body myositis.

The tumour chapter—an all embracing 200 pages with more than 3000 references (I lost count)—is again quite masterly. The bread and butter tumours are capably described, and there are instructive and useful accounts of other important areas, familial tumours, metastatic disease, etc. Again, the narrative is as contemporary as a large text can be, and more up to date than most, with succinct descriptions of the NF siblings neurofibromin and merlin, and of their biology, as far as is known. Surprisingly, in this genomics chapter, paraneoplasia is perhaps a little brief.

It would be unforgivable also to omit mention of the chapter on peripheral neuropathy (Thomas, Landon, and King). Just 100 pages long, this yet again is a joy to read. The first fifth is devoted exclusively to a description of the normal peripheral nerve, an outstanding account. The whole chapter is (predictably) beautifully illustrated, with authority spread deep and thick and even across the whole of the peripheral nervous system, from new immunological concepts in relation to inflammatory neuropathies, to the molecular genetic advances in inherited nerve disease.

So, it is not easy to criticise. I managed to amass a perfectly miserable haul of just one typo (though quite a howler—BAI for BAIOL—in a bold, italicised, large font header). The editing is lightly but highly effectively addressed, and there are very few outright omissions. I could find no account of Hashimoto’s encephalopathy, which is a shame; I suspect many years of further use might fail to add appreciably to this one omission.

This is such a good book. Do buy one. It is well worth the investment, and will stand by you and repay you all the days of your working life.

NEIL J SCOLDING
neurovascular clinic and stroke unit, how to overcome resistance to change, how to participate in or set up large multicentre trials etc. Whether you read this book will largely depend on your point of view.

LIZ WARBURTON


In choosing the title for this book, the editors have wisely avoided the use of the term “neuropsychiatry”, which in Britain, at least, implies a primarily psychiatric audience. I think that this book should be read by a much wider audience, including neurologists interested in behaviour and cognition. There are relatively few books available that bridge this important divide. The editors have assembled an impressive international cast who cover most of the hot topics at the interface of neurology and psychiatry.

The first section is dedicated to the frontal lobes with contributions from neuropsychology and frontal lobe abnormalities on structural scanning in schizophrenia. The second section deals with basal ganglia disorders with excellent overviews of neuropsychological findings and behavioural psychopharmacology. The third section is dedicated to memory and its disorders, with extremely readable overviews of advances and controversies in the neuropsychology of memory and clinical disorders. The fourth section deals with psychiatric manifestations of patients with a known brain pathology and structural imaging in the psychoses. Stricter editorial intervention could have avoided some redundancy and overlap with an earlier chapter. Section five covers for what is for many people the central ground of neuropsychiatry—namely, epilepsy—with excellent accounts of the behavioural and psychiatric changes seen in the context of chronic epilepsy. The sixth section takes a developmental perspective, particularly related to schizophrenia, and the final two chapters of the book deal with advances in brain imaging, namely magnetic resonance spectroscopy and imaging of patients with hallucinations.

The editors have deliberately decided not to write a comprehensive textbook, but rather to choose areas of advance and controversy, and in doing so have produced a very readable text. The book is in many ways a celebration of the immense contributions of Professor Alwyn Lishman to the study of the brain and mind. I can thoroughly recommend it to everyone working in this exciting area.

JOHN HODGES
Facial diplegia with paraesthesias: facial nerve enhancement in three dimensional MRI

AKINORI HOZUMI, NOBUHIRO YUKI, KAORU YAMAZAKI and KOICHI HIRATA

J Neurol Neurosurg Psychiatry 1999 66: 688
doi: 10.1136/jnnp.66.5.688

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