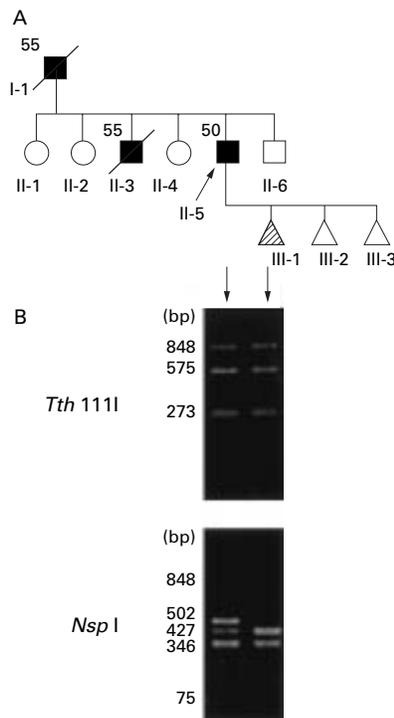


## LETTERS TO THE EDITOR

### Familial Creutzfeldt-Jakob disease with D178N-129M mutation of *PRNP* presenting as cerebellar ataxia without insomnia

Fatal familial insomnia (FFI) is a prion disease clinically characterised by progressive insomnia and dysautonomia, and associated with an aspartic acid to asparagine mutation at the codon 178 (D178N) of the prion protein gene (*PRNP*).<sup>1</sup> This mutation is also associated with familial Creutzfeldt-Jakob disease (CJD). These phenotypes have been held to depend on the polymorphism at the codon 129. FFI and CJD phenotypes are associated with methionine (129M) and valine (129V) polymorphisms, respectively.<sup>2</sup> However, the diverse phenotypes can be associated with D178N-129M genotype.<sup>3,4</sup> We here report on a Japanese family with D178N-129M genotype presenting cerebellar ataxia without overt insomnia.

The pedigree of this family is depicted in the figure. Patient 1 (II-5), a 50 year old man, a proband, noted an unsteady gait in October 1997 and difficulty in speech in December



**Pedigree of the family and genotypes.** (A) Pedigree of the family. Squares, males; circles, females; triangles, either sex (to protect the confidentiality of the family, the sexes of these people are not shown). Filled symbols, affected; shaded symbols, genotype only examined; slashed symbols, deceased; numbers, ages of onset. (B) *Tth* 1111 and *Nsp* I restriction analyses of the 848 bp open reading frame of *PRNP*. The *Tth* 1111-non-digested band of 848 bp indicates D178N mutation. The *Nsp* I-non-digested band of 502 bp indicates 129V polymorphism and the 427 bp band 129M polymorphism. The 75 bp band is too thin to be visible.

1997. These symptoms worsened rapidly. He had no episodes of insomnia, hallucination, or involuntary movement. On admission, he was normal in general condition, well oriented, and cooperative, but slightly restless. The Wechsler adult intelligence scale revised (WAIS-R) score was normal (verbal IQ 108 and performance IQ 95). He showed saccadic ocular movements and nystagmoid movements on lateral gaze. His speech was explosive and scanning. Myoclonus was not evident. The muscle tone and strength were normal. He presented moderate bilateral limb ataxia. He could barely stand and walk on a wide base, and tandem gait was impossible. The deep tendon reflexes were normal in his arms and mildly brisk in his legs without Babinski's sign. Sensory examination was normal. Autonomic signs were absent. Routine laboratory and CSF examinations were normal. An EEG showed a background of 9 Hz  $\alpha$  activities spreading to the anterior regions without periodic synchronous discharges (PSDs). The sleep EEG overnight for 3 days showed a normal sleep pattern in which spindles, K complexes, slow activities, and REM sleep were seen. Brain MRI showed mild cerebellar atrophy. Single photon emission CT (SPECT) using [<sup>99m</sup>Tc]-HMPAO showed hypoperfusion in the bilateral frontal lobe and left parietal region, and left striatum. One year after the onset, he still did not develop either dementia or myoclonus.

In July 1995, patient 2 (II-3), an elder brother of patient 1 developed an ataxic gait and forgetfulness at the age of 55 years followed by dysarthria within a month. He had limb ataxia in his arms. The deep tendon reflexes were normal in his arms and mildly brisk in his legs without Babinski's sign. In November 1995, EEG showed diffuse intermittent slow activities without PSDs. In January 1996, he developed akinetic mutism and myoclonic jerks. Brain CT demonstrated moderate cerebellar atrophy. He presented a decorticate posture and died of respiratory failure 7 months after the onset.

Patient 3 (I-1), the father of patient 1, developed an ataxic gait and dementia at the age of 55. He died of an unknown cause after a clinical course of 12 months.

The 848 bp open reading frame of *PRNP* was amplified by polymerase chain reaction (PCR) using peripheral leucocyte DNA. The mutation at the codon 178 and the polymorphism at the codon 129 were screened by restriction analyses with *Tth* 1111 and *Nsp* I as described elsewhere.<sup>5</sup> The D178N mutation abolishes a *Tth* 1111 site. The restriction analysis of the PCR product shows a non-digested 848 bp fragment in the mutant allele and 575 and 273 bp ones in the normal allele. As shown in the figure, the *Tth* 1111 digestion generated three fragments of 848, 575, and 273 bp in patient 1 and his child (III-1), indicative of both having a heterozygous D178N mutation. The 129V polymorphism abolishes one of the two *Nsp* 1 sites in the PCR product. The restriction analysis shows 502 and 346 bp fragments in the 129V allele, and 427, 346, and 75 bp ones in the 129M allele. Four fragments were detected in patient 1 and three smaller fragments in his child, which indicated that patient 1 was heterozygous for 129V and 129M and that his child was homozygous for 129M. The sequencing of PCR products demonstrated that D178N mutation and 129M polymorphism were on the same allele in patient 1.

Rapidly progressive cerebellar ataxia was present in two generation of this family. Patient 2 presented progressive dementia and

myoclonus, which suggested a diagnosis of familial CJD. The FFI mutation on the 129M allele was found in the examined members of this family. All the patients, however, lacked insomnia clinically, and EEG showed a normal sleep pattern in patient 1. Although pathological findings were not assessed, SPECT in patient 1 did not disclose abnormalities in the thalamus, usually involved in FFI. The phenotype in this family was clearly different from that of FFI. Thus, the supposed dependence of the phenotypes with the FFI mutation on the polymorphism at the codon 129 was not true of the present family. It was already reported in white people that the clinical presentations associated with the FFI genotype are diverse, including cerebellar ataxia, dementia, and autonomic abnormalities with or without insomnia.<sup>3,4</sup> Our findings support the notion that the phenotypic variability in the FFI genotype exists throughout various ethnic backgrounds, and emphasises the heterogeneity of inherited prion disease.

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### Postmalaria neurological syndrome: a case of acute disseminated encephalomyelitis?

We report on a 30 year old woman presenting with neurological dysfunction 8 weeks after complete recovery from *Plasmodium falciparum* malaria. Magnetic resonance imaging during her illness showed multifocal white matter abnormalities. She made a full recov-

ery without any specific treatment. Repeat MRI 6 months after her acute illness showed complete resolution of all lesions. Although the term postmalaria neurological syndrome has been used to describe such cases, the clinical and radiological findings are indistinguishable from those seen in acute disseminated encephalomyelitis.

The term postmalaria neurological syndrome (PMNS) was first introduced in 1996.<sup>1</sup> The syndrome has been defined as the acute onset of neurological or neuropsychiatric symptoms in patients recently recovered from *Plasmodium falciparum* malaria who have negative blood films at the time of onset. This therefore distinguishes it from cerebral malaria, which occurs during parasitaemia. The time from eradication of the systemic parasitaemia to the development of this syndrome can be up to 9 weeks (median 4 days).<sup>1</sup> The prevalence of PMNS in patients with *Plasmodium falciparum* malaria is 0.12%. PMNS is 300 times more common in patients with severe rather than uncomplicated malaria.<sup>1</sup> The reported clinical features include generalised convulsions, acute confusional state, acute psychosis, and tremor. The range of neurological manifestations of PMNS is probably wider and includes cerebellar ataxia (first reported in 1986),<sup>2</sup> motor aphasia, and generalised myoclonus.<sup>3</sup> Most cases made a complete recovery without specific treatment.

We report a case of PMNS where MRI was performed during and 6 months after the period of acute neurological dysfunction. The similarities between PMNS and acute disseminated encephalomyelitis (ADEM) are discussed.

A 30 year old woman was admitted to hospital after returning from a holiday in Kenya. She complained of rigors, sore throat, and shortness of breath. On the day of admission she had become jaundiced. She had not taken any malaria prophylaxis before or during the holiday. A blood film showed 29% falciparum malaria parasitaemia.

She was treated with intravenous quinine, doxycycline, exchange transfusion, and, subsequently, erythrocytapheresis. She remained conscious throughout the acute illness and there was no clinical evidence of cerebral malaria. Her illness was complicated by myocarditis and transient renal impairment. She

was discharged 24 days after admission having made a full clinical recovery.

Two months after discharge she was readmitted. Her partner reported that she had apparently been normal since discharge up until 3 weeks previously. She had become increasingly lethargic and was sleeping for up to 18 hours per day. She had also become agitated, exhibited odd behaviour, and at times experienced language difficulties. Twenty four hours before her admission she had woken up with a severe headache associated with nausea, profound confusion, and inability to recognise her long term partner or her parents.

Initial assessment on admission showed the severe confusion to have largely resolved although she still exhibited inappropriate behaviour and was very apprehensive and restless. Neurological examination disclosed brisk reflexes with no focal neurological deficit. Soon after admission she had a tonic-clonic convulsion. She was treated with phenytoin, intravenous acyclovir, and broad spectrum antibiotics.

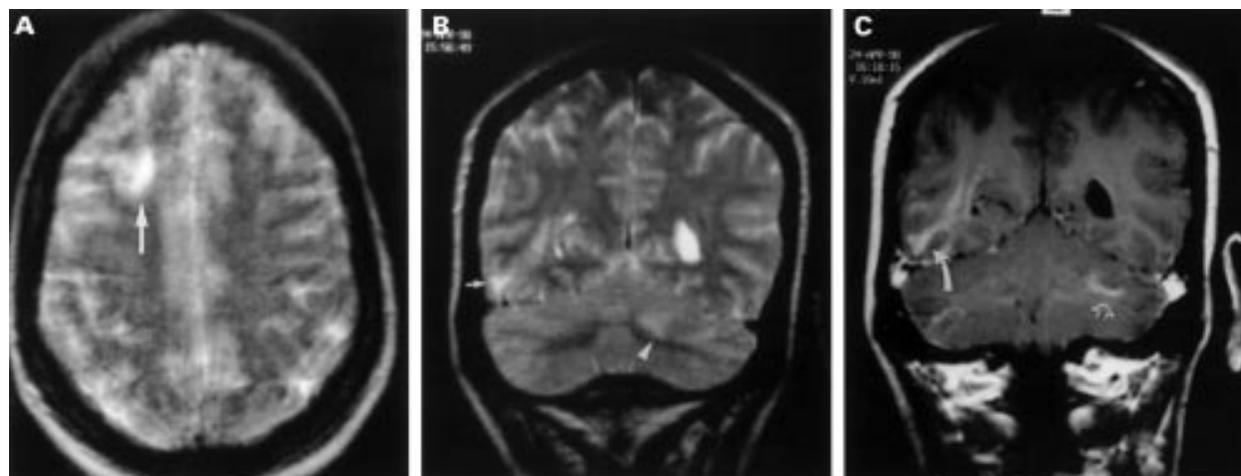
Full blood count, blood film, urea and electrolytes, and random blood glucose were normal. Liver function tests showed slightly raised transaminases. A cranial CT showed no significant abnormalities. Examination of the CSF showed 200x10<sup>6</sup>/l cells, 22 of which were white cells (all lymphocytes) and no xanthochromia. Protein in CSF was raised at 1.4 g/l (normal <0.4 g/l). Brain MRI was performed on a 1.5 Tesla Siemens magnetic system. T2 weighted images of the brain showed areas of high signal in the subcortical white matter of the right frontal and posterior portion of the right temporal lobes (figure A). These were not associated with a mass effect. There was also increased signal in the white matter of the left cerebellar hemisphere (figure B). After intravenous gadolinium DTPA there was contrast enhancement of all areas with white matter signal change (figure C). An EEG showed a large excess of background activity with frequent runs of high voltage rhythmic slow/sharp activity, in keeping with an encephalopathy. Bacterial, viral, and mycobacterial cultures of the CSF and polymerase chain reaction for herpes virus were negative. Autoimmune and vasculitis screens were also negative.

As there was clinical evidence of improvement after the MRI she was not given steroids. She gradually improved over the next week and was discharged home 14 days after admission with no neurological deficit and with complete resolution of her confusional state.

Neurological assessment 6 months after this admission showed her to be normal. Repeat MRI with intravenous contrast on this occasion showed complete resolution of the abnormal findings.

Changes in MRI in PMNS have been reported to date only once, in a case that responded to steroid treatment.<sup>3</sup> The MRI findings in this patient, as in the case previously reported, suggest a multifocal white matter inflammation. This explains the wide range of neurological manifestations reported so far. The aetiology of PMNS is unclear. In cerebral malaria sequestration of knob bearing parasitised red cells within the cerebral vessels can result in local ischaemic damage.<sup>4</sup> This mechanism however cannot be implicated in PMNS where, by definition, no parasitised red cells are present. Plasma and CSF concentrations of cytokines (tumour necrosis factor and interleukins 2 and 6) are raised in patients with severe malaria.<sup>5</sup> Tumour necrosis factor has been implicated in neurotoxicity.<sup>6</sup> These cytokines may persist within the circulation even after eradication of the parasites but, more importantly, they can be found in higher concentrations in the serum samples of patients with PMNS compared with concentrations present during the recovery period.<sup>3</sup> The observed time to neurological dysfunction after eradication of the parasite and the reported response to steroid treatment<sup>3</sup> are supportive evidence of an immunological mechanism. There are no reports in the literature of acute disseminated encephalomyelitis (ADEM) in association with the use of quinine, doxycycline, or after erythrocytapheresis.

There are some similarities between PMNS and ADEM. ADEM is a multifocal, monophasic, demyelinating disease characteristically occurring 1 to 3 weeks after a viral or, occasionally, bacterial infection or vaccination. Most patients with ADEM make a full recovery. In severe cases corticosteroids can be of help. Brain MRI usually shows widespread lesions in the white matter of the



(A) Axial T2 weighted image showing high signal in right frontal white matter (white arrow). (B) Coronal T2 weighted image showing high signal in white matter of right temporal lobe (small white arrow) and left cerebellar hemisphere (white arrow-head). (C) T1 weighted coronal image following intravenous gadolinium DTPA showing enhancement in the white matter of the right temporal lobe (curved white arrow) and left cerebellum (open white arrow).

brain or the spinal cord. Distinction from multiple sclerosis can be difficult at the onset but the clinical history, the course of the disease, the lack of relapses, and the resolution of the lesions on repeat MRI are useful distinguishing features. The similarities between PMNS and ADEM are striking: latency from infection to neurological dysfunction, multifocal neurological deficits, response to steroids, good prognosis, identical MRI findings, and now evidence of complete resolution of such lesions on MRI.

This is the first case report of PMNS showing spontaneous and complete resolution of not only the clinical but also the MRI abnormalities. There are no identifiable clinical or radiological features that can distinguish PMNS from ADEM. *Plasmodium falciparum* malaria should therefore be added to the list of infections able to precipitate ADEM.

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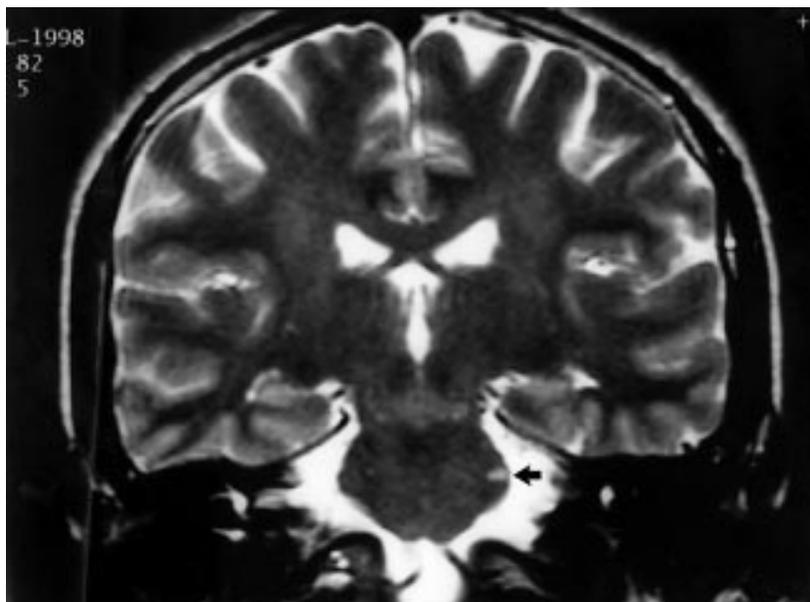
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### Trigeminal sensory neuropathy: anatomico-physiological correlation

The widespread use of MRI, allowing accurate localisation of brain lesions, particularly within the brainstem, tends to overshadow the usefulness of electrophysiology in evaluating functional loss. This is the case of the blink reflex which explores trigeminal and facial nerves, and the brainstem. Discrete lesions at sites along the structures involved in the reflex arc are associated with particular abnormalities of the blink reflex.<sup>1</sup> Here we describe a patient with an isolated trigeminal sensory neuropathy in whom an abnormal blink reflex predicted the localisation of a brainstem lesion.

A 35 year old man reported acute onset of painless paraesthesiae in the ophthalmic territory of the left trigeminal nerve. Examination showed minimal hypaesthesia in the first division of the left trigeminal nerve, with preserved corneal reflex and with no other cranial nerve involvement, nor signs of long tract dysfunction. The blink reflex showed a



(A) Brain MRI shows hyperintensive lesion (arrow).

consistent absence of RI response on the orbicularis oculi ipsilateral to the stimulated left supraorbital nerve. Stimulation of the right supraorbital nerve evoked normal R1 and R2 (ipsilateral and contralateral) responses. Brain MRI showed no supratentorial lesions. The only abnormality was a small hyperintense area in T2 weighted sequences in the left lateral upper pons, close to the entrance of the trigeminal nerve, slightly lateral to the principal sensory trigeminal nucleus (figure). Paraesthesiae resolved in 1 week, and there was full recovery of the R1 component of the blink reflex.

This case illustrates the anatomical and functional correlation between a focal demyelinating area next to the principal sensory trigeminal nucleus and the absence of the first component of the blink reflex. The R1, initially thought to be a myotatic response, is a cutaneous oligosynaptic reflex, the afferent arc of which travels in the supraorbital nerve and the efferent arc through the facial nerve. The central integration of this R1 component occurs at the level of the upper pons between the principal sensory nucleus of the trigeminal nerve and the nucleus of the facial nerve.<sup>2</sup> Indeed, there is a correlation between the presence of a delayed (or absence) R1 response in patients with multiple sclerosis and clinical signs of pontine lesions.<sup>3</sup> Studies of single pontine lesions demonstrated by MRI, or necropsy, and abnormal blink reflex have not been reported previously, although patients with isolated trigeminal sensory neuropathy and brainstem vascular lesions have been described.<sup>4,5</sup> On the other hand, the R2 component of the blink reflex, a polysynaptic reflex, is integrated in the spinal nucleus of the trigeminal nerve establishing bilateral connections with facial nuclei in the pons. This is consistent with preserved ipsilateral and contralateral R2 responses in our patient. The present case further supports the concept that the absence of the first response of the blink reflex is highly suggestive of a pontine lesion, close to, or within, the principal sensory nucleus of the trigeminal nerve. It also illustrates the usefulness of a simple elec-

trophysiological test in the evaluation of reversible dysfunction of the trigeminal nerve.

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### Unilateral eyelid retraction

Two muscles are involved in upper eyelid elevation: the tarsal smooth muscle of Müller that has an accessory role limited to the tonic control of eyelid position, and the levator palpebrae, a skeletal muscle innervated by a subdivision of the oculomotor nerve.<sup>1</sup> The levator palpebrae shares several features with the superior rectus. Both muscles are often activated in conjunction, allowing for eyelid coordination during vertical eye movements, they have common embryological stages,<sup>2</sup> and their motor neurons remain close to each other from the orbit to the mesencephalon. This anatomical parallelism persists at the nuclear level, at least in lateral eyed mammals. In these species, both levator palpebrae and superior rectus nuclei are paired and have crossing axons.<sup>1</sup> However, in higher frontal eyed mammals, levator palpebrae innervation is provided by a single medial

nucleus, the central caudal nucleus, although the crossed pattern of innervation of the superior rectus remains.<sup>3</sup> Anatomical studies have shown that, in most frontal eyed mammals including primates, cell bodies of both levator palpabrae are bilaterally distributed and totally intermixed within the central caudal nucleus.<sup>3</sup> Furthermore, branching axons—that is, levator motor neurons connected with both levator palpabrae, are absent,<sup>3</sup> or extremely rare (2%).<sup>4</sup> Very little is known about the premotor network that controls the central caudal nucleus. A recently identified region in the rostral mesencephalon, medial to the rostral interstitial nucleus of medial longitudinal fasciculus, sends pathways to the central caudal nucleus, and could provide an excitatory signal for the upper eyelid, involved in eyelid coordination.<sup>5</sup> Another structure, the nucleus of the posterior commissure probably provides inhibitory inputs to the central caudal nucleus, as a lesion of this region results in upper eyelid retraction.<sup>6</sup> Each nucleus of the posterior commissure is connected with its contralateral counterpart through the posterior commissure, but does not project directly to the central caudal nucleus. Linkage between the nucleus of the posterior commissure and levator palpabrae motor neurons could be realised in the so called supraoculomotor area.<sup>6</sup> This region, located dorsolaterally to the oculomotor nucleus, within the periaqueductal grey, receives nucleus of the posterior commissure afferents and contains dendrites coming from central caudal nucleus cell bodies.<sup>6</sup> However, the exact pattern of connectivity between the nucleus of the posterior commissure and levator palpabrae neurons within the supraoculomotor area is unknown.

We here report on a patient with a circumscribed brainstem infarction and a consecutive nuclear oculomotor nerve syndrome with normal ipsilateral eyelid position and motility and contralateral eyelid retraction. This unusual pattern of eyelid dysfunction allows for deductions on supranuclear central caudal nucleus pathways involved in levator palpabrae inhibition.

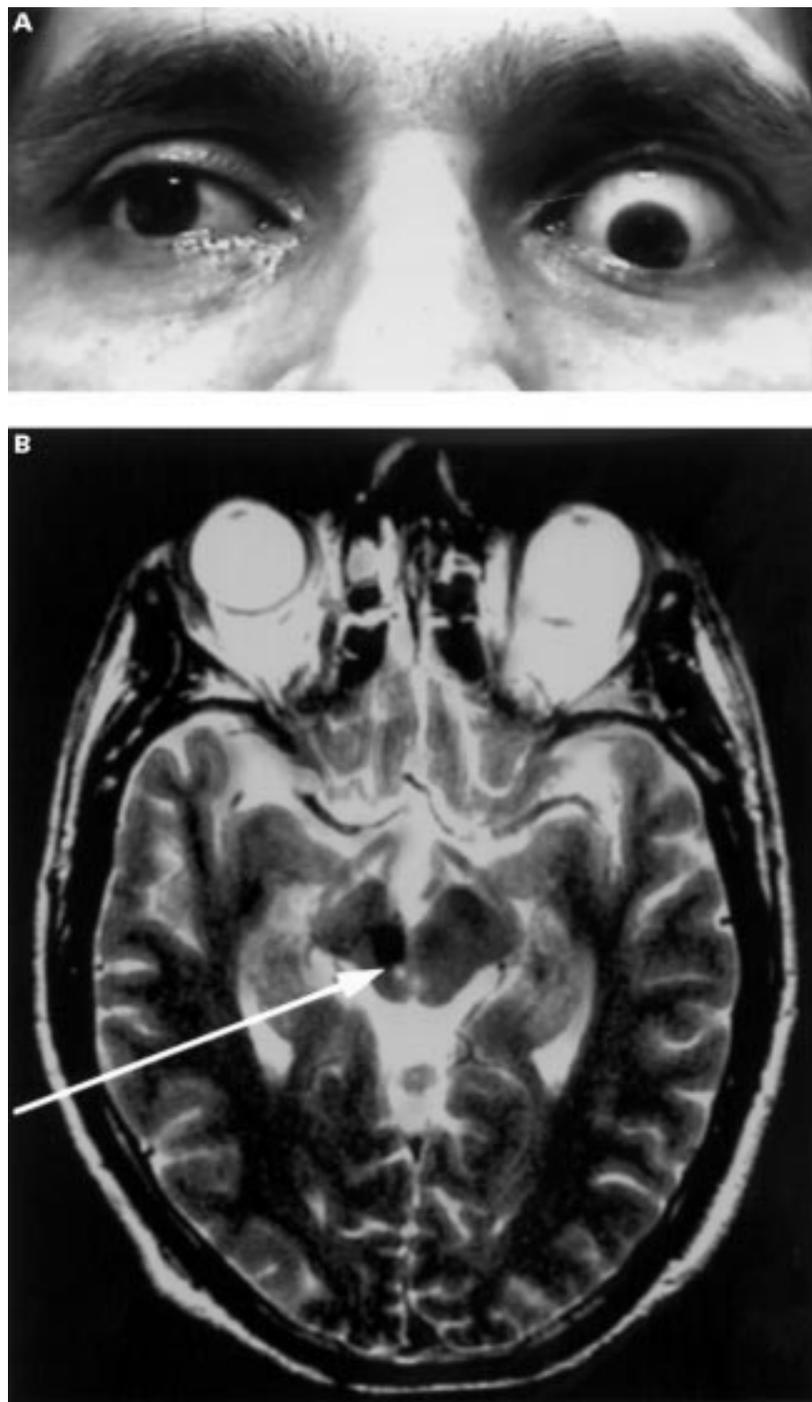
A 44 year old man was admitted after sudden onset of a left hemiplegia. A cerebral CT showed a right thalamopeduncular haematoma. Neuro-ophthalmological examination showed a right sided oculomotor palsy, with a large 5 mm non-reactive pupil, and a vertical gaze and adduction palsy. However, there was no ptosis: the right eyelid had a normal position in resting condition, and showed upward and downward displacements during attempted vertical eye movements. Abduction was normal. On the left side, there was a tonic downward deviation of the eye that could not be elevated above the horizontal plane, even during vertical oculocephalic manoeuvres. Downward movements, abduction, and adduction were normal. The pupil was of normal size (2.5 mm) and reactive to light. The eyelid was markedly retracted, a 4 mm band of upper sclera being uncovered in resting conditions (figure A). Manual opening or closure of the right eyelid did not influence lid retraction on the left side.

When the patient was seen on follow up 2 months later, the ocular motor syndrome was unchanged. Written consent was obtained from the patient for photographs. Brain MRI was performed and showed a lesion in the right thalamus and in the right paramedian mesencephalon. At this level, the lesion

involved the region of the red nucleus and extended posteriorly towards the sylvian aqueduct but remained anterior to the posterior commissure (figure B).

The clinical features of this patient are consistent with a lesion of the right oculomotor nucleus.<sup>1</sup> Complete elevation palsy on the side contralateral to the lesion is explained by the crossed innervation of the superior rectus. The downward deviation of the eye on the normal side has been previously reported and results from the unopposed action of the intact left inferior rectus muscle. Normal reactivity of the left pupil indicates that the lesion did not reach the unpaired Edinger-

Westphal nucleus, located at the rostral pole of the oculomotor nucleus. Therefore, right-sided mydriasis resulted from an involvement of ipsilateral Edinger-Westphal nucleus efferent fibres. Conversely, absence of ptosis on the right side indicates that the central caudal nucleus and its efferent fibres (in the right oculomotor nerve) were intact. Such levator sparing in patients with an oculomotor nucleus lesion has already been reported,<sup>7</sup> and is probably related to the mediocaudal location of the central caudal nucleus. The striking clinical feature of this patient was the existence of a contralateral eyelid retraction without ipsilateral ptosis, a condition that has



(A) patient with unilateral eyelid retraction on the right side. Note normal eyelid position on the left side. (B) T2 weighted axial MRI (TR/TE 5000/96.8) showing a left sided mesencephalic circumscribed lesion involving the red nucleus and impinging on the region of the oculomotor nucleus (arrow).

not been previously reported in the context of a stroke. This retraction was unlikely to result from an levator palpebrae overactivation (as it would be expected according to Hering's law) as it was not influenced by manual elevation of the contralateral lid.<sup>1</sup>

Various patterns of eyelid disorders may be encountered in patients with focal mesencephalic lesions. Ptosis may be unilateral when central caudal nucleus efferent fibres are damaged, or bilateral, if the central caudal nucleus itself is involved.<sup>1</sup> A bilateral eyelid retraction results from a lesion that involves either the posterior commissure or the nucleus of the posterior commissure itself.<sup>6</sup> Lastly, a mixed pattern, the plus-minus lid syndrome, consists in ipsilateral ptosis and contralateral eyelid retraction.<sup>8</sup> It is ascribed to a lesion involving both central caudal nucleus efferent (ipsilateral ptosis) and afferent (contralateral eyelid retraction) fibres.<sup>8</sup> However, in this latter case, the ipsilateral ptosis could mask an eyelid-retraction. Therefore, in our patient, absence of ipsilateral ptosis shows that, at least in this case, eyelid retraction was strictly contralateral. According to anatomical data, it may be suggested that eyelid retraction in our patient resulted from a lesion involving central caudal nucleus afferent fibres—that is, inputs from the nucleus of the posterior commissure, most probably in the region of the supraoculomotor area.<sup>6</sup> It may thus be inferred that inhibitory connections between the nucleus of the posterior commissure and central caudal nucleus (through the supraoculomotor area) are unilateral, and crossed. A similar crossed pattern may also exist for excitatory afferents to the central caudal nucleus, as hemispheric lesion resulting in contralateral ptosis have been reported.<sup>1</sup>

Inhibition of the levator palpebrae occurs mainly in conjunction with orbicularis oculi activation,<sup>1</sup> a phenomenon that is controlled by monocular pathways. Thus, this push-pull system would have an homogenous unilateral organisation. Lastly, the crossed pattern of these inhibitory connections is reminiscent of the crossed levator palpebrae innervation which exists in phylogenetically lower mammals.<sup>9</sup>

In summary, it may be inferred from this finding and from anatomical data that the central caudal nucleus receives inhibitory inputs from the contralateral nucleus of the posterior commissure, and that lesion of these pathways leads to contralateral eyelid retraction.

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#### Behçet's syndrome may present with partial seizures

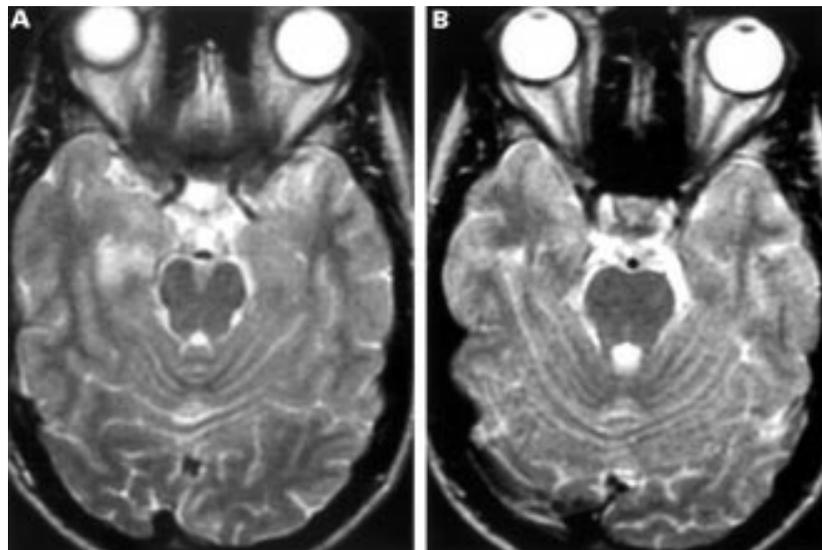
A 25 year old right handed male shop assistant presented with seizures, visual problems, and malaise. The first symptoms were arthralgia and fatigue shortly followed by a bifrontal headache. A few days later he developed a visual disturbance that he described as peripheral blurred patches in both visual fields similar to the effect of staring into a bright light. About 2 weeks from the onset of symptoms he was driving when he had numerous episodes of déjà vu and three episodes of a pungent sickly smell. He then lost consciousness and crashed his car into a public house without serious injury. An off duty nurse witnessed a generalised tonic-clonic seizure at the time. He was admitted to hospital and investigated but no diagnosis was made. The headache stopped completely in a month; the visual defects improved slightly but persisted. Six months later he had a relapse with recurrent headaches, pyrexia, and enlargement of the scotoma in the right eye and he was readmitted. He had had recurrent oral ulceration for 3 years and psoriasis since childhood, but no genital ulceration, red eyes, or venous thrombosis.

On examination he had a low grade pyrexia. General examination was otherwise normal with no evidence of pathergy at sites of needle pricks, genital ulceration, arthritis, or venous thrombosis. He was oriented with

no meningism. Acuity was 6/5, N4.5 bilaterally. Colour vision was normal. In the left eye there was a partial superior scotoma, in the right eye a superior nasal scotoma. Fundoscopy showed specific features of the uveitis of Behçet's syndrome. This consisted of multiple pale yellow patches of retinal infiltration lying deep to retinal vessels. Eye movements were normal. Pupils were equal and reactive with no afferent pupillary defect. The rest of the cranial nerve examination, gait, and limb examination was normal.

Biochemistry, liver function, thyroid function, coagulation studies, serum electrophoresis, serum ACE, B<sub>12</sub>, folate, and plasma amino acids were all normal. Haematology showed a slight lymphopenia of 1.0 (1.5-4.0) and slightly increased erythrocyte sedimentation rate at 19. Autoantibody profile, RF titre, and syphilis serology were negative; CSF pressure was normal, but analysis was abnormal with 20 white cells (93% lymphocytes, not reactive) and a slightly increased protein of 0.88 g/l, glucose was 3.0 mmol/l (serum 4.2 mmol/l). The CSF had no oligoclonal bands; CSF ACE and cytology were normal. Chest radiography, ECG, transthoracic ECHO, and extracranial magnetic resonance angiography (MRA) were normal. An EEG showed a mild asymmetry of  $\alpha$ -rhythm being lower amplitude and less well formed on the left but no epileptiform features. Brain MRI was performed on two occasions. The MRI at presentation showed two small focal T2 hyperintense lesions in the head of the right caudate nucleus and more diffuse signal change in the right mesial temporal lobe within the head and body of the right hippocampus (figure). There was no evidence of venous sinus thrombosis.

A diagnosis of Behçet's syndrome with neurological complications was made on the basis of typical retinal lesions, multiple focal CNS lesions, recurrent mouth ulceration and a constitutional disturbance. Prednisolone was started at a dose of 40 mg daily, his symptoms rapidly improved and so combination immunosuppression was not used. A second MRI, a year later, showed that the lesions previously seen in the caudate had disappeared and that in the mesial temporal region had undergone a marked reduction in size (figure). There have been no more seizures and he has remained off antiepileptic medication.



T2 weighed MRI showing a mesial temporal lobe lesion with resolution a year later.

Behçet's syndrome is a multisystem inflammatory disorder of unknown aetiology.<sup>1</sup> It is a disorder of young adults with a male preponderance. There is a striking geographical variation in prevalence. The triad of oral and genital ulceration with hypopyon iritis is classic but neurological involvement is the most serious manifestation. There is no specific laboratory test and so diagnosis is made on clinical features. The International Study Group for Behçet's syndrome diagnostic criteria are recurrent oral ulceration plus two from recurrent genital ulceration, eye lesions, skin lesions, or positive pathergy test. Strict use of these criteria leads to underdiagnosis and it is accepted, as in this case, that experienced clinicians may make the diagnosis on the more unusual features of the syndrome. In the British series neuroBehçet's syndrome usually manifested as a subacute brainstem meningoencephalitis, occasionally with involvement of hemispheres or spinal cord. Brain MRI demonstrates lesions in about three quarters of patients with neuroBehçet's disease.<sup>1</sup>

To our knowledge this is the first report of Behçet's syndrome presenting with seizures. The phenomenology of the seizure cluster at presentation suggests that the focus was the lesion in the medial temporal lobe identified on the first MRI. As this lesion has regressed the prognosis for further seizures should be good and to date there has been no recurrence. There are occasional reports in the literature of seizures associated with Behçet's syndrome. A 35 year old man developed frank seizures coincident with a myocardial infarction and ventricular tachycardia after 2 years of Behçet's syndrome.<sup>2</sup> A 38 year old woman also developed generalised seizures and recurrent status epilepticus 3 years before a diagnosis of Behçet's syndrome.<sup>3</sup> A patient in a Turkish series was reported to have myoclonic jerks.<sup>4</sup> In these reports the phenomenology of epilepsy was not presented and no clear relation could be made to the disease process. There have been a few reports of EEG abnormalities in some severely affected cases consisting of periodic lateralising epileptiform discharges (here herpes simplex encephalitis was the main differential diagnosis),<sup>5</sup> but mostly of non-specific EEG changes without prognostic value, as seen in the present case.

In summary, this case illustrates an unusual neurological complication of Behçet's syndrome. Diagnosis was made on the basis of a typical posterior uveitis, recurrent mouth ulceration, multiple focal CNS lesions on MRI, and constitutional upset. He presented with complex partial and secondary generalised seizures with a medial temporal lobe lesion on MRI that disappeared 6 months later.

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### Morphological abnormalities of hepatic mitochondria in two patients with spinocerebellar ataxia type 7

The dominantly inherited spinocerebellar ataxias (ADCAs) are a clinically and genetically heterogeneous group of neurodegenerative disorders characterised by premature neuronal loss in the cerebellum. The cardinal manifestations are ataxia, dysarthria, dysmetria, and intention tremor. These clinical findings are associated with varying degrees of other neurological symptoms due to degeneration of other components of the nervous system. The similarity in the clinical presentation of the ADCAs to the mitochondrial cytopathies is widely recognised. Ptosis, ophthalmoplegia, pyramidal and extrapyramidal symptoms, optic atrophy, retinopathy, dementia, and peripheral neuropathy may variably occur in both disorders. Patients with an ADCA are therefore often investigated to exclude a mitochondrial disease.

The ADCAs are divided into three groups (ADCA I, II, III) on the basis of associated findings.<sup>1</sup> ADCA II is characterised by the presence of a retinopathy.<sup>2</sup> It is caused by mutations (unstable trinucleotide expansion) in the coding region in a single gene, SCA7, on the short arm of chromosome 3.<sup>3</sup> The protein product, ataxin-7, has a nuclear localisation.<sup>3</sup> Clinically, patients with this rare condition present with visual impairment and ataxia, which may be associated with dementia, ophthalmoplegia, spasticity, and extrapyramidal symptoms.<sup>2</sup> We have identified two SCA7 families and report here on the finding of abnormal hepatic mitochondria in the index cases of the two families. This is a hitherto undescribed finding.

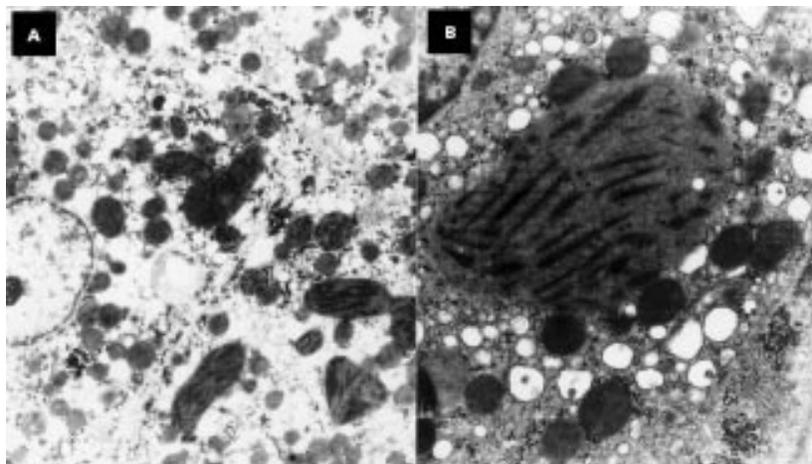
Patient 1 was a 20 year old black woman who presented with progressive ataxia and

visual loss beginning at the age of 16 years. She had severely impaired mental functions, bilateral ptosis with external ophthalmoplegia, bilateral peripapillary and macular degeneration, distal weakness (bilateral foot drop) with depressed reflexes but intact sensation (nerve conduction studies were not done), and abnormal movements including a fixed torticollis to the right with ocular and palatal myoclonus. Brain CT and MRI showed marked cortical, cerebellar, and brainstem atrophy. Routine screens to exclude acquired causes of ataxia and retinal degeneration were carried out. Serum concentrations of pyruvate, lactate, vitamin E, and a fasting lipogram, liver function tests, assays for  $\beta$ -galactosidase,  $\alpha$ -galactosidase, sphingomyelinase,  $\beta$ -glucosidase hexosaminidase, long chain fatty acids, copper, and caeruloplasmin were normal. Urine screened for organic amino acids, copper and heavy metals was normal or negative. There were no acanthocytes. Her CSF was normal. Histological examination of skeletal muscle showed no ragged red fibres (with Gomori trichrome stain) and no morphologically abnormal mitochondria on electron microscopy. Results from cytochrome oxidase, NADH-TR, succinic dehydrogenase, oil red O, and PAS stains were normal. Skin, conjunctival, and rectal biopsies were histologically normal and normal on electron microscopy. A liver biopsy was histologically normal. There was no fatty steatosis. On electron microscopy morphological abnormalities of the mitochondria were present. The figure shows the abnormalities of the mitochondria in shape and size. Paracrystalline inclusions, forming so called parking lot bodies were demonstrated. At least 50% of the mitochondria showed these abnormalities.

Blood samples were screened for the SCA 1, SCA 3/MJD (Machado-Joseph disease), and SCA 7 trinucleotide expansions. Polymerase chain reaction analysis of her DNA showed a SCA 7 CAG repeat length of 81 (normal 7 to 17 repeats<sup>3</sup>).

Her mother and two other siblings are affected. They did not have biochemical, histological, or genetic investigations.

Patient 2 was a 25 year old black woman who presented with progressive visual failure. She was ataxic and had bilateral peripapillary and macular degeneration with spasticity and



Photograph showing ultrastructural abnormalities of hepatic mitochondria. In (A) the abnormalities of size and shape are shown. The mitochondria are seen to contain amorphous paracrystalline and laminated inclusions. In (B), a higher power magnification of these shows the presence of laminated paracrystalline type inclusions in a mitochondrion.

1 Kidd D, Steuer A, Denman AM, *et al.* Neurological complications in Behçet's syndrome. *Brain* 1999;122:2183-94.

bilateral ptosis without ophthalmoplegia. She had clinical depression but had no evidence of a dementia. Brain CT showed marked brainstem and cerebellar atrophy. Investigations were carried out as described in patient 1. All tests, including histological analyses were normal or negative, apart from the hepatic electron microscopy. This showed identical mitochondrial abnormalities. Polymerase chain reaction analysis of her DNA showed a SCA 7 CAG repeat length of 53. Her mother is clinically affected but declined investigations.

The electron microscopical changes identified in the two index cases are widely recognised as indicative of mitochondrial disease. They are usually identified in skeletal muscle as the prototype tissue involved in the mitochondrial encephalopathies. The failure to identify the abnormalities in the other tissues sampled, especially skeletal muscle, may reflect selection bias. Biochemical and molecular studies have not yet been undertaken.

Abnormal mitochondria (with paracrystalline inclusions) are not present in normal liver tissue but can be seen in various conditions, including alcoholic liver disease, diabetes mellitus, hepatocellular carcinoma, hepatocellular adenoma, Wilson's disease, and drugs including the oral contraceptive rifampicin, phenobarbital, and steroids.<sup>4</sup> These were all excluded in the two index cases. In terms of neurological diseases, Okamura *et al*<sup>5</sup> described a patient with congenital oculoskeletal myopathy, diarrhoea, deafness, and cardiac and endocrine abnormalities in whom abnormal mitochondria were found in skeletal muscle as well as in liver cells.

In SCA7, Cooles *et al*<sup>6</sup> described a family in whom abnormally large mitochondria with irregular cristae were identified in the skeletal muscle of three affected members. Intramitochondrial inclusion bodies as seen in our patients were not present. Forsgren *et al*<sup>6</sup> described a large SCA7 pedigree in whom electron microscopy of skeletal muscle in affected people showed uneven distribution of mitochondria, subsarcolemmal accumulations of small rounded mitochondria, areas devoid of mitochondria, and frequent autophagic vacuoles. In a severely affected child in this family, reduced activities of complex IV and to a lesser extent of complex I were found. In the above reports, hepatic tissue was not examined.

Ptosis and ophthalmoplegia were present in both our index cases and were also prominent in the affected family members (not described here). These are frequent in the mitochondrial encephalopathies but occur variably in SCA7. Enevoldson *et al*,<sup>2</sup> in their extensive review of the clinical features of patients with SCA7, describe ptosis as being "quite common". In the family of Cooles *et al*<sup>6</sup> ptosis was a feature of the disease. The external ophthalmoplegia is more uniformly present in cases described in the literature.<sup>2</sup>

The patients described here and those described in the literature suggest mitochondrial dysfunction in SCA 7. The protein ataxin-7, however, has a nuclear localisation.<sup>3</sup> In Friedrich's ataxia, an autosomal recessive triplet repeat disorder with an unstable mutation of the X25 gene on chromosome 9q13-q21.1, the protein product frataxin is a nuclear encoded mitochondrial protein.<sup>7</sup> Mitochondrial dysfunction is therefore implicated in its pathogenesis. Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant trinucleotide expansion

disorder.<sup>8</sup> Mitochondrial abnormalities have been found in the skeletal muscle of patients with OPMD.<sup>8</sup>

The relevance of mitochondrial abnormality, in patients with SCA7 as well as other triplet disorders, is therefore intriguing and requires further investigation.

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### Cervical syringomyelia at the C7-C8 level presenting with bilateral scapular winging

Scapular winging is a neurological sign specifically caused by weakness of the serratus anterior, trapezius, or rhomboid muscles.<sup>1,2</sup> Trauma, complications of surgery, myopathies, or peripheral nerve diseases are the major causes. We report on a patient with bilateral scapular winging as the presenting symptom of cervical syringomyelia at the C7-C8 spinal cord segments.

This 38 year old carpenter complained of progressive involuntary movements of the right arm associated with arm and shoulder pain for the past 3 years. Involuntary movements were provoked by writing and similar activities. The patient was suspected of having a psychogenic movement disorder.

Examination disclosed normal cranial nerve functions, mild hypertrophy of the right arm muscles, bilateral scapular winging of the serratus anterior type, and mild paresis of the left and right serratus anterior and triceps muscles. The left triceps tendon jerk was attenuated, but the remaining deep tendon reflexes of the arms were normal. The knee and ankle jerks were brisk and symmetric. Examination of sensation, including thermesthesia, was normal.

Skilled manual activities involving the right hand such as picking up a pen or holding a cup of coffee stereotypically induced brisk adduction of the right arm combined with pronation of the hand. Rhythmic alternating movements of the normal left hand were regularly interrupted when action dystonia of the right hand began; indeed this suggested psychogenic dystonia.



Sagittal T1 weighted image (SE 500/25 ms) disclosing a small intramedullary cervical syrinx at the level of the vertebral body C7/T1.

Electromyographic examinations showed chronic neurogenic changes of both serratus anterior and triceps muscles. Nerve conduction and transcranial magnetic stimulation studies were normal. Median and ulnar nerve somatosensory evoked potentials showed significant attenuation on the left. Laboratory tests and cranial MRI were normal. Cervical MRI showed a small central cord lesion at the level of vertebral body C7, probably cervical syringomyelia (figure), as well as a hindbrain hernia. The patient was followed up for 2 years, and his condition remained stable.

It is generally thought that three spinal roots, C5, C6, and C7, contribute to the long thoracic nerve which supplies the serratus anterior muscle.<sup>3</sup> Isolated root lesions of C7-Th1 are not a generally accepted reason for prominent weakness of the serratus anterior muscle,<sup>1</sup> but several cases with unilateral scapular winging as the presenting sign for C7 radiculopathy have been published.<sup>3,4</sup> Clinical presentation of this patient was atypical for C7 radiculopathy. With the exception of the triceps muscles, he had no

clinical involvement of other muscles supplied by the C7 or C8 segments.

Lesions of the spinal anterior horns in syringomyelia usually cause amyotrophy that begins in the small muscles of the hands, ascends to the forearms, and ultimately affects muscles of the shoulder girdle. The clinical presentation of our patient with isolated paresis of the serratus anterior and triceps muscles is therefore very unusual.

Apart from the intramedullary syrinx at C7/T1, cervical MRI also demonstrated a small hindbrain hernia. Syringomyelia usually arises as a result of an associated anomaly,—for example, the Arnold-Chiari malformation; the demonstrated hernia thus may be the aetiology of the syrinx.

Another interesting finding in this patient is the combination of syringomyelia with movement disturbances. Dystonia and other movement disorders in syringomyelia are rare, but have been recorded.<sup>5,6</sup> Nevertheless, careful clinical examination suggested psychogenic dystonia in this patient.

The present case illustrates that a central lesion presumably of the C7 and C8 spinal cord segments may damage the serratus anterior motor nucleus on both sides and thus may cause bilateral scapular winging thereby mimicking a neuromuscular disorder.

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**Focal neuropathy associated with cutaneous necrosis at the site of interferon-β injection for multiple sclerosis**

Interferon-β is the first approved treatment for relapsing multiple sclerosis. Although generally well tolerated, it is sometimes associated with cutaneous reactions at the injection site. To decrease local side effects, it has been suggested that injection sites in the belly, the thigh, and the arms are regularly changed. These cutaneous reactions range from slight erythema to necrosis. We report the first mononeuropathy associated with local adverse reaction after interferon-β injection.

A 39 year old woman had a 15 year history of multiple sclerosis, and a 3 year history of secondary progressive phase (EDSS=6). She

had been treated for 3 years with subcutaneous interferon-β 1b (Betaferon®) every other day, when a painful violaceous, livedoid pattern on the skin of the posterior aspect of the right upper arm appeared, at a site of injection at the mid-portion of the humerus. Two days later, a necrotic ulcer (diameter 10 mm, depth 2 mm) occurred. Concomitantly, she experienced tingling on the dorsal aspect of the thumb without motor or reflex abnormalities. The livedo lasted a month, and the spontaneous ulcer healed in the same time. The sensory dysfunction recovered 10 months after onset. The following laboratory tests were negative or normal: glycaemic tests, antinuclear antibodies, rheumatoid factor, complement fractions, cryoglobulin, thyroid tests, and anticardiolipin antibodies.

Radial neuropathy was confirmed by neurophysiological testing performed 3 months after the onset. A motor conduction block (80% reduction of the compound muscle action potential amplitude) was found on the right radial nerve at the level of the injection site related necrosis. In addition, cutaneous thermal thresholds (TSA-2001, Medoc, Ramat, Israel) in the right radial nerve territory were significantly higher than the contralateral ones, whereas radial sensory nerve action potential amplitudes were normal and symmetric (right 82 μV; left 92 μV). Ten months after onset, the conduction block had disappeared and thermal thresholds were normal.

Cutaneous necrosis occurred in 1% to 3% of patients treated by interferon-β1b.<sup>1</sup> Necrosis may be favoured by an inadequate injection technique, not rotating the injection sites, or absence of heating of the diluent before the injection. Cutaneous necrosis associated with interferon-β injection is thought to potentially combine inflammatory and ischaemic local damage.<sup>2</sup> The pathophysiological mechanism of the focal neuropathies can only be hypothetical, but several features of our case suggest an ischaemic mechanism. Conduction block in motor nerve fibres is a feature of ischaemic nerve injury.<sup>3</sup> The discrepancy between thermal sensory impairment and normal sensory nerve action potential amplitude is consistent with the higher susceptibility to ischaemia of smaller nerve fibres;<sup>4</sup> Raynaud's phenomenon has been recently reported as the first evidence of ischaemic lesion induced by interferon-β injection for multiple sclerosis.<sup>5</sup>

This led us to avoid some recommended sites of injection, which correspond to the anatomical course of peripheral nerves. These include the posterior aspect of the arm to preserve the radial nerve, the lateral abdominal wall, and close to the anterior superior iliac spine, to preserve the lateral femoral cutaneous nerve, and the upper aspect of the buttock to preserve the sciatic nerve.

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**Treatment with intravenous prednisone and immunoglobulin in a case of progressive encephalomyelitis with rigidity**

The progressive encephalomyelitis with rigidity syndrome (PEMRS) is a rare neurological disorder that can be considered as the most severe form of the "stiff person" syndrome<sup>1,2</sup> although other authors suggest that it may be a distinct entity.<sup>3</sup> Pathogenesis is far from being clearly defined, but some studies point to humoral immunity as having an important role. Antiglutamic acid decarboxylase (anti-GAD) antibodies have been found to be present in about 40% of patients with stiff person syndrome.<sup>4</sup> Treatment is very difficult and in the only case reported so far in which intravenous immunoglobulin has been used the response was poor.<sup>2</sup> We report a case of PEMRS with anti-GAD antibodies that had an excellent response to intravenous immunoglobulin.

A 67 year old woman was admitted to our hospital with a 9 month history of progressive gait disturbance and painful leg contractions. Family history was negative for neurological disorders. General examination was unremarkable. On neurological examination she showed marked stiffness in her legs and painful spasms; these appeared spontaneously but could also be elicited by external events such as touch, noise, and frightening. The examination was otherwise normal.

Brain and spinal MRI did not show any abnormality. Both needle EMG and nerve conduction were normal except for spontaneous firing of motor units. Blood tests including vitamin B<sub>12</sub> and folic acid, C<sub>3</sub>, C<sub>4</sub>, thyroid hormones, antithyroglobulin antibodies, syphilis serology, and CSF examination were all within normal limits. Anti-GAD autoantibodies were positive, both in serum (1/16000 IU with histochemistry and 1/30325 IU/ml with radioimmunoassay (RIA) and in the CSF (1/40 IU with histochemistry).

For unknown reasons, a week after admission the clinical course changed: the patient seemed to be confused, became disoriented, and her consciousness was clearly impaired. The spasms were more severe and neurological examination showed bilateral pyramidalism with Babinski's sign. The clinical picture corresponded to a progressive encephalopathy. This was confirmed by EEG (generalised slow waves). We started treatment with valproate, gabapentin, and diazepam but lack of improvement led us to try intravenous immunoglobulin (0.4 g/kg/24 hours for 5 days and then the same dosage every 2 days) together with intravenous methylprednisolone (80 mg/24 hours). A positive response appeared at the 5th day. After 7 days of treatment she regained normal consciousness and did not show any spasms.

However, 6 weeks later the patient presented with gait disturbances again. Anti-GAD autoantibodies were again positive in serum (1/8000 IU with histochemistry and

1/36250 IU/ml with RIA) and in the CSF (1/20 IU with histochemistry). For this reason, immunoglobulin (0.4 g/24 hours for 5 days) was used again with prednisone (60 mg/24 hours orally (the previous dose had been reduced to 40 mg/48 hours)). Six months after admission she continued free of spasms, with a total independence for daily life activities, but on examination she had a mild loss of memory and a mild loss of strength in both hands.

The aetiology of both stiff person syndrome and PEMRS remains unknown although an autoimmune mechanism has been suggested. Therefore, plasmapheresis, intravenous immunoglobulin, and diazepam have been empirically proposed as treatments of stiff man syndrome.<sup>2-6</sup> PEMRS could be responsive to plasmapheresis and immunosuppression,<sup>7</sup> but to our knowledge, this is the first case of PEMRS reported in which intravenous immunoglobulin has been successfully used. It seems possible that the successful outcome should be due to the association of prednisone with intravenous immunoglobulin.

The initial clinical picture of this case resembled closely the stiff person syndrome, even with a positive determination of anti-GAD autoantibodies in CSF. PEMRS features appeared some days later. The patient was treated with diazepam, gabapentin, and valproate without any response; moreover, she developed severe muscle spasms and a confusional state. Five days after starting treatment with intravenous immunoglobulin and steroids, the patient reached a normal level of consciousness and the leg cramps disappeared, although she had a moderate loss of strength in her hands and a mild memory loss. When she was discharged 4 weeks later on prednisone (80 mg/day) these were her only symptoms. However, when prednisone was decreased some cramps reappeared and prednisone had to be increased again to the previous dose and an immunoglobulin cycle was needed, obtaining a positive response. She has been free of cramps since then.

We think that intravenous immunoglobulin associated with prednisone could be a useful and life saving treatment for patients with PEMRS.

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## CORRESPONDENCE

### Benign multiple sclerosis? Clinical course, long term follow up, and assessment of prognostic factors

The study by Hawkins and McDonnell<sup>1</sup> found that in multiple sclerosis, women were more likely than men to have a benign course and that young subjects had a more benign course than older subjects with multiple sclerosis. These findings prompt the question: Do postmenopausal women with multiple sclerosis on estrogen replacement therapy do better than those not taking such therapy? Axonal damage is now recognised to be an important determinant of disability in multiple sclerosis (reviewed in Scolding and Franklin<sup>2</sup> and de Stefano et al<sup>3</sup>) and myself and colleagues have recently reported more severe axon loss in crossed corticospinal tracts in the spinal cord in men than women who died with a diagnosis of multiple sclerosis.<sup>4</sup> Estrogen has growth promoting effects on some neurons<sup>5</sup> and thus may have the capacity to protect axons from damage in multiple sclerosis. It might be predicted that estrogen replacement therapy could have a beneficial effect on postmenopausal women with multiple sclerosis.

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- 1 Hawkins SA, McDonnell GW. Benign multiple sclerosis? Clinical course, long-term follow up, and assessment of prognostic factors. *J Neurol Neurosurg Psychiatr* 1999;67:148-52.
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- 5 McEwen BS, Alves SE. Estrogen actions in the central nervous system. *Endocrin Rev* 1999;20:279-307.

#### The authors reply:

We appreciate the observations of Esiri on our paper. The reasons for the more benign course experienced by both younger and female patients are unclear but the hormonal theory she outlines is interesting and certainly has merit.

It has previously been demonstrated that in experimental allergic encephalomyelitis the animal model of multiple sclerosis, estrogen therapy significantly reduces the severity of the disease compared with placebo treatment and it has further been postulated that this

favourable response may be mediated by increased production of Th2 cytokines such as interleukin-10.<sup>1</sup> More pertinent has been the findings on the effect of pregnancy on multiple sclerosis where relapse rate declines antenatally only to increase again during the first 3 months postpartum.<sup>2</sup> Interestingly, relapse rates are at their lowest during the last trimester of pregnancy when estrogen levels are reaching their peak.

The hormonal theory and variation in estrogen levels with age might also help to explain the significant proportion of patients in our study who, after an initially benign course, subsequently slip into the secondary progressive phase and seem to deteriorate at a rate similar to those in the "non-benign" category. Unfortunately we are not placed to confirm whether early menopause is associated with a poorer prognosis or if those taking estrogen replacement therapy enjoy a better prognosis and this is clearly worthy of further study.

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- 2 Confavreux C, Hutchinson M, Hours MM, et al. Rate of pregnancy-related relapse in multiple sclerosis. *N Engl J Med* 1998;339:285-91.

### Predicting survival using simple clinical variables: a case study in traumatic brain injury

Signorini et al<sup>1</sup> developed a prognostic model to predict survival at 1 year for patients with traumatic brain injury. A strong point is that this model uses variables which are easy and cheap to measure. A thorough statistical analysis was performed, including tests for goodness of fit and checks for influential observations. The model was also validated externally in a more recent group of patients. However, during the external validation the Hosmer-Lemeshow statistic showed a significant lack of calibration ( $p < 0.0001$ ).

This implies that the model does not give accurate predictions of the survival of "new" patients. The lack of calibration is especially due to an overly pessimistic prediction in the patients with a poor prognosis but also to a too optimistic prediction for patients with a better prognosis (fig 2).<sup>1</sup> This is typical for "overfitting"—that is, that a model tends to predict too extreme probabilities in new patients.

Overfitting can be limited by several procedures. One of them is that, as a rough estimate, no more than  $m/10$  predictor degrees of freedom (df) should be analysed to construct a multiple regression model, where  $m$  is the number of events (for example, deaths).<sup>2</sup> As 87 patients died within 1 year,  $87/10 = 8.7$  df could be examined during the course of analysis without risk of overfitting. In the paper 6 df were used by the final multivariate prognostic model. However, age was fitted as a piecewise linear variable after using a generalised additive model, requiring an unknown number of df, but always more than one. Furthermore, we assume that easy to achieve variables such as sex (1 df) and cause of injury (3 df) were considered but dropped during model construction. Also some of the candidate variables originate from combined variables when, after initial assessment, it seemed that some categories could be collapsed. Altogether this means that probably much more than 8.7 df were examined.

The overfitting could have been corrected by multiplying each regression coefficient in the model with a shrinkage factor. This factor can be estimated by a heuristic formula,<sup>3</sup> by cross validation, or by a bootstrap resampling procedure. This can be done with the Design library,<sup>4</sup> which was already used by the authors. The shrinkage factor is close to unity when there is no overfitting. When the selection of predictors is unstable or predictors have small effects, a lower shrinkage factor might be found—for example, 0.8.

We regret that the model is presented as giving “reasonable accurate predictions of long term survival”, especially because the external validation showed a significant lack of calibration. Correction with a shrinkage factor would have resulted in a recalibration of the probability of survival in the nomogram presented in the paper (fig 3)<sup>1</sup> and in the formula used in a subsequent paper.<sup>3</sup>

We hope that modern modelling techniques will increasingly be applied in clinical prediction problems such as traumatic brain injury, such that prognostic models are developed that reliably support the physician in clinical decision making.

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- 3 Van Houwelingen JC, le Cessie S. Predictive value of statistical models. *Stat Med* 1990;8: 1303-25.
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- 5 Signorini DF, Andrews FJD, Jones PA, *et al.* Adding insult to injury: the prognostic value of early secondary insults for survival after traumatic brain injury. *J Neurol Neurosurg Psychiatry* 1999;66:26-31.

Signorini *et al* reply:

Hukkelhoven *et al* give a thorough and constructive criticism of the statistical procedures used to construct the model presented in the paper. Their main points of concern regard the effective number of degrees of freedom (df), possible corrections to the apparent overfitting, and the usefulness of the model for individual predictions in specific patients.

It is true that the 6 df present in the final model do not reflect the total uncertainty present in the model, and that some preprocessing of individual predictors was performed to derive appropriate functional forms. The rule of thumb regarding the number of predictor variables which can be assessed in a multivariate model is a guideline, and it should always be remembered that the reason behind it is to prevent false positive findings and hence spurious associations between predictors and outcomes. It is directly analogous to the 5% significance level for hypothesis testing, and we worry that in its increasing prevalence in the literature it is becoming similarly dogmatic. We

do not think that we have indulged in any data-dredging to construct these models, and are confident that the false association rate is small. To fully incorporate the overall uncertainty into the final model would perhaps involve methods discussed by Draper,<sup>1</sup> with a corresponding increase in the complexity of the modelling process.

The use of shrinkage estimators to prevent overfitting is of course a valuable tool, yet as Hukkelhoven *et al* point out, there are several options for their calculation and little guidance as to which should be used in a particular circumstance. They are available within the design library used to build our model, but the model building process as described in the original paper is achievable using any standard statistical software package. The purpose of the paper was to demonstrate what we think of as a sensible approach, and to go beyond what is possible in standard software would be to dilute that message.

Finally, the model perhaps should not be described as providing “accurate” predictions of long term survival, as the out of sample calibration was not good. From a discrimination point of view, however, the out of sample performance was adequate, and this serves to illustrate that the uses to which a model will be put should play a part in the model building process. Whether calibration (individual predictions) or discrimination (case mix adjustment) is more important can result in different models from the same training set.

One of the most important points of the paper was to stress that there is a lot more to proper statistical model building than clicking the correct menu option in a statistical package. We would hope that this correspondence has emphasised the need for a certain level of statistical knowledge and experience in the analysis of any research data. We agree wholeheartedly with the views expressed in the correspondents’ final paragraph.

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- 1 Draper D. Assessment and propagation of model uncertainty. *Journal of the Royal Statistical Society, Series B* 1995;57:45-97.

### Distinctions between critical illness polyneuropathy and axonal Guillain-Barré syndrome

In this letter we comment on the publication of Yuki and Hirata who postulate a possible relation between critical illness polyneuropathy and axonal Guillain-Barré syndrome.<sup>1</sup> The authors mentioned a nosological relation, which at that time still had to be demonstrated by the presence of antiganglioside antibodies in the serum of patients with critical illness polyneuropathy. Critical illness polyneuropathy is a neuromuscular disorder that has been recognised in critically ill patients.<sup>2</sup> The clinical picture consists of difficulty in weaning from the artificial respirator, tetraparesis, and muscle wasting of the limbs. The tendon reflexes are mostly decreased or absent. The neurophysiological examination shows an axonal polyneuropathy and sometimes myopathic altered motor unit potentials. The morphological features in the nerve point to a primarily distal axonal degeneration of motor and sensory fibres. Muscle biopsy shows scattered atrophic fibres

in acute denervation and grouped atrophy in chronic denervation. Also, necrotic muscle fibres can be found suggesting the contribution of a myopathy or a primary myopathy.<sup>3</sup> On clinical and electrodiagnostic grounds neuromuscular complications in the critically ill patients may be due to a polyneuropathy or myopathy. Because it is not always possible to differentiate between an axonal motor neuropathy and myopathy, we prefer to use the descriptive term critical illness polyneuropathy and myopathy (CIPNM).

To test the hypothesis of Yuki and Hirata we studied the serum of eight patients obtained during the acute phase of CIPNM and from two controls, which were patients that were also on the artificial respirator and critically ill. In all 10 patients sepsis or systemic inflammatory response syndrome occurred. The serum samples were tested for IgG and IgM reactivity against gangliosides GM1 and GD1a. In none of these samples could any reactivity be detected. Therefore, it is unlikely that in these Dutch patients with CIPNM, axonal damage is mediated through anti-GM1 or anti-GD1a antibodies as was suggested by the authors.

To distinguish CIPNM from the acute motor axonal variant of Guillain-Barré syndrome the following characteristics may be useful:

- Guillain-Barré syndrome is the primary neurological reason of admission on the intensive care unit; CIPNM on the other hand develops during a patient’s stay on the intensive care unit for another reason
- Infectious symptoms such as fever and diarrhoea have usually subsided before the clinical features of Guillain-Barré syndrome appear
- The characteristic alterations in the CSF of patients with Guillain-Barré syndrome, with a raised protein and normal to slightly increased cell count
- The possibility of detecting IgG antibodies against GM1, GM1b, GD1a, and GalNac-GD1a as immunological markers in the serum of patients with axonal Guillain-Barré syndrome.

Electrodiagnostic changes in Guillain-Barré syndrome occur in both sensory and motor nerves in about 80% of the patients in the western world. In CIPNM there is a predominantly motor dysfunction in both the clinical and electrodiagnostic evaluations.

During the progression of Guillain-Barré syndrome the demyelinating features of the nerve conduction study may change into a secondary axonal pattern. In axonal Guillain-Barré syndrome slow nerve conduction velocity remains in some patients and the initial needle EMG study lacks spontaneous activity.<sup>4</sup> In CIPNM phrenic nerve conduction studies usually show no significantly prolonged latencies.<sup>5</sup>

Severe autonomic disturbances are more common in patients with Guillain-Barré syndrome after the polyneuropathy has developed than in patients with CIPNM.<sup>3</sup>

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#### New hope for patients with pure lower motor neuron syndromes

Readers of the editorial by Wokke and van den Berg<sup>1</sup> may be left with the impression that the immunoglobulins could provide hope for the future for patients with pure lower motor neuron syndromes but no conduction block. Their evaluation of the results obtained by Ellis *et al*<sup>2</sup> in four of the total series of 10 patients may tend towards overoptimism, however.

We agree with their second conclusion regarding the criteria for referring this subgroup of patients with lower motor neuron disease to a highly specialised centre for further analysis. However, we would recommend referral for all patients with motor neuron disease, especially in cases in the initial stages or in atypical forms, in which the diagnosis may be difficult if strict criteria are applied, given the complexity and multidisciplinary management of this condition and the difficulty of the decision regarding when and to whom pharmacological and life sustaining therapy should be applied.

Great care must be taken to avoid misdiagnosis in the selection of candidates for therapy, as the high cost of long term treatment does not justify indiscriminate immunoglobulin use. A critical reading of work of Ellis *et al* shows that only three responding patients of the 10 treated presented an objective improvement in the pinch and grip myometries and no statistically significant modification in the MRC scale or significant objective improvement in the paired *t* test was found.

Finally, of the 10 patients with lower motor neuron syndrome included in the assay, there were four cases of amyotrophic lateral sclerosis (ALS), one of spinal muscular atrophy (SMA), one doubtful case of multifocal motor neuropathy (MMN), and four probable cases of MMN at follow up. These last five presented no conduction blocks and only one had anti-GM1 antiganglioside antibodies.

If we accept and if we can demonstrate the usefulness of immunoglobulins in lower motor neuron forms, two questions arise. Firstly, can we accept the existence of MNN without conduction block? Katz *et al* tried to answer this question by proposing that conduction block was only one of many electrodiagnostic features in a segmental demyelination. They advocated the inclusion of other features, such as conduction velocity, temporal dispersion, delayed F wave responses, and prolonged distal latencies.

Ellis *et al* admit that their study was not designed as an electrophysiological study, and that the exhaustive nerve conduction studies described by Lang *et al* and Katz *et al* were not performed.<sup>3,4</sup> Secondly, if we accept that we are dealing with patients lower motor neuron disease, we would have to re-examine the hypothesis that has been considered to be

flawed regarding the role played by immune mechanisms in motor neuron diseases.<sup>5</sup>

Another point about which we have our reservations is that it cannot be affirmed that the non-introduction of this treatment leaves the patients at the mercy of the disease's natural course. The problem lies in the difficulty in diagnosing these patients, especially those who present neither conduction blocks nor anti-GM1 antiganglioside antibodies. As we have previously stated, the final diagnosis in 50% was ALS or SMA. Given these results, it seems more reasonable to persist with differential diagnosis by magnetic resonance neurography and repetition of neurophysiological examinations, including magnetic transcortical stimulation.

Patients with motor neuron disease and their relatives, who have been anxiously waiting for a breakthrough in treatment, have been disappointed time and again in recent years by promises regarding therapies that have been both expensive and of little use. It can only be hoped that the immunoglobulins will improve this situation, and that our scepticism is mistaken.

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## BOOK REVIEWS

**Intra-Operative Diagnosis of CNS Tumours.** Edited by TIM H MOSS, JAMES A R NICOLL, JAMES W IRONSIDE. (Pp193 £99.00). London: Arnold, 1997. ISBN 0-340-67737-6.

This is a handsome and liberally illustrated guide to smear and frozen section diagnosis in neuropathology. This aspect of practice remains a central part of a clinical neuropathologist's role and this book can be recommended to trainees and practitioners for its wealth of illustration and practically oriented text. It is particularly useful to see a wide range of appearances for each tumour illustrated—for example, 20 figures illustrating metastatic tumours, 13 illustrating pituitary adenomas, and 38 illustrating various grades of astrocytic tumours. This enables the less readily diagnosed examples to be considered as well as more typical varieties. Typical varieties tend to be the only ones illustrated in a less specialised text. There are

#### Yuki replies:

Critical illness polyneuropathy, a complication of sepsis and multiple organ failure, may be a common cause of the difficulty of weaning patients in critical care units from the ventilator.<sup>1</sup> Its aetiology has yet to be determined and needs to be clarified to treat such patients more effectively. Critical illness polyneuropathy and Guillain-Barré syndrome are both monophasic illnesses of acute onset, characterised by limb weakness and areflexia. Whereas classic pathological studies of Guillain-Barré syndrome show demyelination and inflammatory infiltrates in peripheral nerves, electrophysiological and pathological studies of critical illness polyneuropathy show the presence of primary axonal degeneration of the peripheral nerves but no evidence of inflammation. The two types of polyneuropathies, therefore, have been considered separate entities, but recent pathological studies have established that there is a primary axonal form of Guillain-Barré syndrome. We mentioned that axonal Guillain-Barré syndrome should be the diagnosis for some patients with critical illness polyneuropathy, and that investigation of the presence of serum IgG antibodies against GM1, GM1b, GD1a, or GalNAc-GD1a (possible immunological markers for axonal Guillain-Barré syndrome) in patients with critical illness polyneuropathy should help test this hypothesis.<sup>2</sup>

I deeply appreciate de Letter *et al* for testing our hypothesis. Some patients with Guillain-Barré syndrome who do carry either anti-GM1 or anti-GD1a IgG antibodies, however, have anti-GM1b, anti-GalNAc-GD1a antibodies, or both.<sup>3,4</sup> I am willing to investigate anti-GM1b and anti-GalNAc-GD1a IgG antibodies in their patients with critical illness polyneuropathy. Further examinations using many more serum samples as well as the additional markers are necessary to reject our hypothesis. If some patients with critical illness polyneuropathy do have those autoantibodies, they would benefit from intravenous immunoglobulin therapy,<sup>5</sup> which is also useful for treating the sepsis associated with critical illness polyneuropathy.

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- 1 Zochodne DW, Bolton CF, Wells GA, et al. Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. *Brain* 1987;110:819-42.

18 chapters that cover each of the main types of tumour encountered as well as providing advice on making and interpreting smears and dealing with lesions that do not smear well. The emphasis is on using smears as standard preparations with frozen sections as back up when required—a procedure that is probably adopted in most neuropathology departments.

The success of a book like this depends crucially on the quality of the photographs. These are, appropriately, all in colour. Many are of excellent quality. Some are intentionally obscure—for example, to make the point that desmoplastic carcinomas may be too tough to examine in smears (fig 18.1). A few have rather poorly defined features and these tend to be illustrations of frozen sections which inevitably lack the crispness of smears. However, even these illustrate the points intended. The legends to the figures are full enough to avoid the need for arrows that might otherwise have obscured the images. There is a useful index, but the book would have benefited from more references—I found only six.

Smear diagnosis is best learnt by doing it, with a sympathetic, experienced colleague at one's elbow. Often this condition cannot be fulfilled and I would strongly recommend this book as a very valuable alternative or adjunct.

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**MRI of the Brain. Normal Anatomy and Normal Variants.** Edited by PATEL and FRIEDMAN. (Pp 480, £61.00) Published by W B Saunders Co, London, 1997. ISBN 0-7216-6945-X.

This book presents the normal anatomy of the brain as seen on MRI studies in a very didactic, well presented, and novel manner. Images are well chosen, and are of high quality. The authors also attempt to relate some of the anatomical structures to their functions and damage of relevant areas to disease processes. The book reflects the hard work and dedication of the authors in pursuing a good radiological-anatomical correlation, something which although being crucial for neuro-radiology, is sometimes forgotten or taken for granted!

The book is divided in 19 chapters, 18 of them covering different anatomical regions of the brain. The last chapter presents some anatomical variants, as well as pitfalls on MRI, which should not be confounded with real lesions. In general, the book will be useful for the training neuroradiologist, and also for all of us dealing with neuroradiology and MRI and having to exercise our anatomical knowledge on a daily basis! Although the authors base the book's structure on classic anatomy, sometimes putting too much emphasis on anatomical classifications that may not be too useful for neuroradiologists nowadays, it results quite enjoyable, easy to read, and a useful teaching tool to have.

Those chapters dealing with the vascular anatomy on MRA are specially useful, in my opinion, since MRA is playing an increasingly more important role in neuroradiology, replacing conventional angiography for many clinical indications.

BEATRIZ GOMEZ-ANSON

**Everything you need to know about Old Age Psychiatry.** Edited by ROBERT HOWARD (Pp292, £45.00) Published by Wrightson Biomedical Publishing, Petersfield, 1999. ISBN1 871816 38 6.

There is a bewildering and almost paralysing amount of information currently aimed at the clinician. The number of journals available seems to increase exponentially often with "evidence based" or continuing professional development in their titles, to impress themselves upon you. Many evenings can be wasted surfing websites purporting to be a valuable source of information for the clinician.

Is there room for such a book as this?

*All you need to know about Old Age Psychiatry* edited by Robert Howard has its roots in the Biannual short course of the same name held at the Institute of Psychiatry in 1998. The Editor states that the course and book have a simple aim, "to provide a current and comprehensive digest of the areas whose rapid development will most affect our work as old age psychiatrists". Contributors to the book are "acknowledged experts" in their field and their grasp of the subject matter is evident.

The book is divided into three sections: basic research in dementia, and the treatment of dementia and functional disorders. Many of the chapters are expected, for example updates in the genetic and molecular biology of Alzheimer disease and recent developments in prion disease and dementia with Lewy bodies. Other chapters are less expected but very interesting and thought provoking—for example, Sir Ludovic Kennedy's chapter arguing for assisted death in dementia, and Robin Jacoby's chapter which pulls together information on forensic psychiatry in old age. Particularly helpful are chapters on treatment resistant depression, ECT, and a review of antidepressants. Overall the book lives up to the editors' stated aims. So when you prioritise your reading and study time this book with its excellent reviews should feature fairly high up your list.

CAROL GREGORY

**Clinical Diagnosis and Management of Alzheimer's Disease, 2nd Edition.** By SERGE GAUTHIER. (Pp386, £65.00). Published by Martin Dunitz, London, 2000. ISBN 1-85317-655-9.

This book is a clear concise and up to date account of current management of Alzheimer's disease. The reader is led through the diagnosis and management of Alzheimer's disease in a readable, well structured, and well presented way. As such, I would envisage that a wide range of health professionals, who have frequent contact with Alzheimer's disease sufferers, including general practitioners, general physicians, geriatricians, specialist nurses, and neurologists, would find this new edition extremely useful.

The text is divided into several sections, from the initial chapter on definitions and diagnostic criteria, to the diagnosis of Alzheimer's disease and differential diagnosis, the evolution of the disease, medical and social management, and finally ethical and

legal issues. The perspective throughout the book is practical, helpful, and informative. For example, the chapter on typical clinical features is full of tables illustrating the symptomatology of the disease. The chapters on structural and functional neuroimaging contain many good quality illustrations and there are also interesting chapters on behavioural problems and functional autonomy. However, perhaps the best section is that on medical management. The confusing issues of the current state of play of drug therapies in Alzheimer's disease are clearly reviewed in a well structured way dealing with symptomatic, stabilisation, and preventative strategies. The social and psychological aspects of the disease are not ignored and the chapters on competence, support of the families, and community services are vital to the comprehensive review of management this book provides.

With the recent explosion in Alzheimer's disease research, the editors may find that there will be the need for frequent new editions. However at present, the wide appeal of this book is guaranteed by the excellent coverage of the clinical and management issues in Alzheimer's disease.

CLARE GALTON

**Dementia Handbook.** By RICHARD J HARVEY, NICK C FOX, and MARTIN N ROSSOR. (Pp 116, 19.95). Published by Martin Dunitz Ltd, London, 1999. ISBN 1-85317-753-9.

Clinically, dementia is an unusual area in that it cannot be pigeon holed into any single specialisation. Gerantologists, neurologists, and psychiatrists all have a part to play in the medical management; while the contribution of neuropsychology, a non-medical discipline, cannot be underestimated. Consequently books which offer a comprehensive patient oriented clinical approach to the subject can be hard to find.

The Dementia Research Group of which the authors are members certainly have the credentials to effect such a synthesis and this book manages to provide a brief but useful synopsis spanning the various fields as well as some areas (for example, support services) usually absent from any medical text. Recent developments in diagnosis and treatment of the dementias have made past algorithms obsolete; especially diagnostic, where the philosophy of the "standard" CAT, thyroid and B 12 assays, and a syphilis test was to exclude rather than establish a diagnosis. In this sense the book is also timely with handy summaries of major categories as well as rare causes of dementia. There are also useful prescribing guidelines for the new anti-dementia drugs.

In attempting to squeeze such a comprehensive checklist into a small space there is the risk of becoming feckless. Thus we learn in the "blood tests" section that HIV testing is indicated "in suspected HIV infection". Likewise such brevity may become overly dogmatic: the reader is advised that echocardiography (oddly listed as a neurophysiological test) should be performed in suspected vascular dementia. But these are only pedantic criticisms for a book which should find a place in the clinic as a practical pocket reference.

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