LETTERS TO THE EDITOR

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

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). 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. However, the diverse phenotypes can be associated with D178N-129M genotype.1,2 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 (I-1), a 50 year old man, a proband, noted an unsteady gait in October 1997 and difficulty in speech in December 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. Routine laboratory and CSF examinations were normal. An EEG showed a background of 9 Hz 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 [99mTc-HMPAO showed hyperperfusion 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 psychosis.

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 intermitten 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 January 1996, he developed akinetic mutism and myoclonic jerks, and his speech was explosive and scanning. As shown in the figure, the Tth 111I and Nsp I digestion generated three fragments of 848, 575, and 273 bp in the mutant allele and 575 and 273 bp ones in the normal allele. As shown in the figure, the Tth 111I digestion generated three fragments of 848, 575, and 273 bp in patient 1 and his child (II-1), indicative of both having a heterozygous D178N mutation. The 129V polymorphism abolishes one of the two Nsp I sites in the PCR product. The restriction analysis shows 502 and 436 bp fragments in the 129M allele, and 427, 346, and 75 bp ones in the 129V 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 generations 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 phenotype 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.3 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 recovery.

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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. 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). 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. 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), motor aphasia, and generalised myoclonus.

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, erythrocytophoresis. 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 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 convolution. 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 elevated bilirubin. Protein in CSF was raised to 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. 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 leucocytes by parasitised red cells within the cerebral vessels can result in local ischaemic damage. 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. Tumour necrosis factor has been implicated in neurotoxicity. 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. The observed time to neurological dysfunction after eradication of the parasite and the reported response to steroid treatment 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 erythrocytophoresis.

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
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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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 correlation between a focal demyelinating area next to the principal sensory nucleus of the trigeminal nerve. It has an accessory role limited to the tonic control of eyelid position, and the leverator palpebrae, a skeletal muscle innervated by a subdivision of the oculomotor nerve. The leverator 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, 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 palpabrae, a skeletal muscle innervated by a subdivision of the oculomotor nerve, and their motor neurons remain close to each other from the orbit to the mesencephalon.


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 leverator palpebrae, a skeletal muscle innervated by a subdivision of the oculomotor nerve. The leverator 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, 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 leverator palpebrae and superior rectus nuclei are paired and have crossing axons. However, in higher frontal eyed mammals, leverator palpebrae innervation is provided by a single medial
nucleus, the central caudal nucleus, although the crossed pattern of innervation of the superior rectus remains. 3 Anatomical studies have shown that, in most frontal eyed mammals including primates, cell bodies of both levator palpebrae are bilaterally distributed and linked with the central caudal nucleus. 3 Furthermore, branching axons—that is, levator motor neurons connected with both levator palpebrae, are absent, 3 or extremely rare (2%). 3 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 the spinal tract, and could provide an excitatory signal for the upper eyelid, involved in eyelid coordination. 3 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. 3 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 palpebrae motor neurons could be realized in the so called supraocular motor area. 3 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. 3 However, the exact pattern of connectivity between the nucleus of the posterior commissure and levator palpebrae neurons within the supracentral 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 palpebrae 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 nerve. 3 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, 9 and is probably related to the medio-caudal 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 palpabre overactivation (as it would be expected according to Hering's law) as it was not influenced by manual elevation of the contralateral lid.

Various patterns of eyelid disorders may be encountered in patients with focal menes-ccephalic lesions. Ptosis may be unilateral when central caudal nucleus efferent fibres are damaged, or bilateral, if the central caudal nucleus itself is involved. A bilateral eyelid retraction results from a lesion that involves either the posterior commissure or the nucleus of the posterior commissure itself.

Lastly, a mixed pattern, the plus-minus lid syndrome, consists in ipsilateral ptosis and contralateral eyelid retraction. It is ascribed to a lesion involving both central caudal nucleus efferent (ipsilateral ptosis) and afferent (contralateral eyelid retraction) fibres. 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 efferent fibres—that is, inputs from the efferent fibres of the posterior commis-sure, most probably in the region of the superuoculomotor area. It may thus be inferred that inhibitory connections between the nucleus of the posterior commissure and central caudal nuclei (through the su-prauoculomotor area) are unilateral, and crossed. A similar crossed pattern may also exist for excitatory afferents to the central caudal nucleus, as hemispheric lesion result-ing in contralateral ptosis have been reported.

Inhibition of the levator palpebrae occurs mainly in conjunction with orbicularis oculi activation, 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.

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.

Behçet’s syndrome may present with partial seizures

A 25 year old right handed male shop assist-ant 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 deja 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 bilater-ally. Colour vision was normal. In the left eye there was a partial superior scotoma, in the right eye a superinioral scotoma. Funduscopy showed specific features of the uveitis of Behçet’s syndrome. This consisted of multi-pel 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 func-tion, coagulation studies, serum electro-pherosis, serum ACE, B12, 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 syphils serology were negative; CSF pressure was normal, but analysis was abnor-mal 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 u-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 symp-toms rapidly improved and so combination immunosuppression was not used. A second MRI, a year later, showed that the lesions pre-viously seen in the caudate had disappeared and that in the mesial temporal region had undergone a marked reduction in size (fig-ure). There have been no more seizures and he has remained off antiepileptic medication.
Behçet’s syndrome is a multisystem inflammatory disorder of unknown aetiology. 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 classsic 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.

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 MRI. As this lesion has regressed on the first MRI. We concluded that the diagnosis was a lateralized EEG abnormality in a case of neuro-Behçet’s syndrome.

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, dystarthis, 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. Postis, 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.

Morphological abnormalities of hepatic mitochondria

The ADCAs are divided into three groups (ADCA I, II, III) on the basis of associated findings. ADCA II is characterised by the presence of a retinopathy. It is caused by mutations (unstable trinucleotide expansion) in the coding region of a single gene, SCA7, on the short arm of chromosome 11. The protein product, ataxin-7, has a nuclear localisation. Clinically, patients with this rare condition present with visual impairment and ataxia, which may be associated with dementia, ophthalmoplegia, spasticity, and extrapyramidal symptoms. We have identified two SCA7 families and report here on the finding of abnormal hepatocellular mitochondria in the index cases of the two families. This is a hitherto undescribed finding.

Photograph showing ultrastructural abnormalities of hepatic mitochondria. In (A) the abnormalities of size and shape are shown. The mitochondria are seen to contain amorphous paracyrstalline and laminated inclusions. In (B), a higher power magnification of these shows the presence of laminated paracyrstalline type inclusions in a mitochondrion.
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 were 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. These were all excluded in the two index cases. In terms of neurological diseases, Okamura et al described a patient with congenital ocularskelatal myopathy, diaphrea, deafness, and cardiac and endocrine abnormalities in whom abnormal mitochondria were found in skeletal muscle as well as in liver cells.

In SCA7, Coeles et al described a family in whom abnormally large mitochondria with intramitochondrial inclusions were identified in the skeletal muscle of three affected members. Intramitochondrial inclusion bodies as seen in our patients were not present. Forsgren et al 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 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, in their extensive review of the clinical features of patients with SCA7, describe ptosis as being “quite common”. In the family of Coeles et al ptosis was a feature of the disease. The external ocularskelatal myopathy is more uniformly present in cases described in the literature. The patients described here and those described in the literature suggest mitochon-
drial dysfunction in SCA 7. The protein ataxin-7, however, has a nuclear localisation. In Friedreich’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. Mitochondrial dysfunction is therefore implicated in its pathogenesis. Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant trinucleotide expansion disorder. Mitochondrial abnormalities have been found in the skeletal muscle of patients with OPMD.

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 characterised by weakness of the serra-
tus anterior, trapezius, or rhomboid muscles. 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. Rhythmical alternating movements of the normal left hand were regularly interrupted when action dystonia of the right hand began; indeed this suggested psychogenic dystonia.

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 vertebreal 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. Isolated root lesions of C7-Th1 are not a generally accepted reason for prominent weakness of the serratus anterior muscle, but several cases with unilateral scapular winging as the presenting sign for C7 radiculopathy have been published.

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, and ischaemic local damage. Conduction block in motor nerve fibres is a feature of ischaemic nerve injury. The present case illustrates that a central disorder that can be considered as the most severe form of the “stiff person” syndrome 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 B12 and folate acid, C3, C4, thyroid hormones, antithyroglobulin antibody, syphilis serology, and CSF examination were all within normal limits. Anti-GAD autoantibodies were positive, both in serum (1/16000 IU/ml 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 encephalomyelitis with rigidity.

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/day 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. Anti-GAD autoantibodies were again positive in the serum (1/8000 IU with histochemistry and ischaemic local damage. The present case illustrates that a central neurological disorder that can be considered as the most severe form of the “stiff person” syndrome 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 B12 and folate acid, C3, C4, thyroid hormones, antithyroglobulin antibody, syphilis serology, and CSF examination were all within normal limits. Anti-GAD autoantibodies were positive, both in serum (1/16000 IU/ml 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 encephalomyelitis with rigidity.

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We thank Dr F Graus (Hospital Clinic i Provincial, Barcelona) for the definition of GAD antibodies.


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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,1 by cross validation, or by a bootstrap resampling procedure. This can be done with the Design library2 of S-Plus, 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) and in the formula used in a subsequent paper.3

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 will support the physician in clinical decision making.

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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.1 The authors mentioned a nosological relation, which at that time still had to be demonstrated. In 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.2 The clinical picture consists of difficulty in weaning from the artificial respirator, tetaaparesis, 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.3

On clinical and electrophysiological grounds neuromuscular complications in the critically ill patients may be due to a myopathy or polyneuropathy. 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, who 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:

1. Infectious symptoms such as fever and diarrhoea have usually subsided before the clinical features of Guillain-Barré syndrome appear
2. The electrophysiological alterations in the CSF of patients with Guillain-Barré syndrome, with a raised protein and normal to slightly increased cell count
3. The possibility of detecting IgG antibodies against GM1, GM1b, GD1a, and Ga1Nac-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 evaluation.

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.4 In CIPNM phrenic nerve conduction studies usually show no significantly prolonged latencies.5

Severe autonomic disturbances are more common in patients with Guillain-Barré syndrome after the polyneuropathy has developed than in patients with CIPNM.6

With the development of chronic critical illness polyneuropathy predominantly sensory symptoms are present, which may result in a higher number of patients with autonomic dysfunction. Patients with polyneuropathy may have a higher incidence of autonomic dysfunction, as demonstrated by the presence of autonomic nervous system dysfunction in patients with Guillain-Barré syndrome.7

The question still remains whether the critical illness polyneuropathy is a separate entity or part of a spectrum of disease associated with critical illness.8


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Yuki replies:

Critical illness polyneuropathy, a complication of sepsis and multiple organ failure, may be a complication of the difficulty of weaning patients in critical care units from the ventilator. 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 classical 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 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. We 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.1,4 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 these autoantibodies, they would benefit from intravenous immunoglobulin therapy,5 which is also useful for treating the sepsis associated with critical illness polyneuropathy.

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New hope for patients with pure lower motor neuron syndromes

Readers of the editorial by Wokke and van den Berg1 may be left with the impression that the immunoglobulins could provide hope for the future for patients with pure lower motor neuron syndromes. Their evaluation of the results obtained by Ellis et al2 in four of the total series of 10 patients may tend towards overoptimism, however. We agree with their 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 the 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 case of 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 anti-ganglioside 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 MMN without conduction block? Katz et al4 tried to answer this question by proposing that conduction block was only one of many electrophysiological features in a segmental demyelination. They advocated the inclusion of other features, such as conduction block, temporal dispersion, delayed F wave responses, and prolonged distal latencies.

Ellis et al admitted 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.4,5 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.1

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 anti-ganglioside 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 transcutaneous 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 TM 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 the use of CT and MRI in frozen section diagnosis in neuroradiology. This aspect of practice remains a central part of a clinical neuroradiologist’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 36 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
Everything you need to know about Old Age Psychiatry. Edited by ROBERT HOWARD (Pp292, £45.00) Published by Wrightson Biomedical Publishing, Petersfield, 1999. ISBN 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 single 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 material 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 where can you find a reading and study time book with its excellent reviews should feature fairly high up your list.

CAROL GREGORY


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 confused 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 GONZALEZ-ANSON


Clinically, dementia is an unusual area in that it cannot be pigeon holed into any single specialisation. Gerontologists, 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. The 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 antide-pressant 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 echo-cardiography (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.

PETER NESTOR
Benign multiple sclerosis? Clinical course, long term follow up, and assessment of prognostic factors
MARGARET ESIRI

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