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*).¹ 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.² However, the diverse phenotypes can be associated with D178N-129M genotype.^{3,4} 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 α 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 [^{99m}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.⁵ 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 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 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.^{3,4} 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.

Y TANIWAKI

H HARA

Department of Neurology, Neurological Institute,
Faculty of Medicine, Kyushu University, Japan

K DOH-URA

Department of Neuropathology

I MURAKAMI

Department of Neurology

H TASHIRO

Department of neuropathology

T YAMASAKI

H SHIGETO

K ARAKAWA

E ARAKI

T YAMADA

Department of Neurology

T IWAKI

Department of neuropathology

J KIRA

Department of Neurology,

Correspondence to: Dr Yoshihide Taniwaki, Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
email taniwaki@enjoy.ne.jp

- Medori R, Tritschler HJ, LeBlanc A, et al. Fatal familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene. *N Engl J Med* 1992;326:444-9.
- Goldfarb LG, Petersen RB, Tabaton M, et al. Fatal familial insomnia and familial Creutzfeldt-Jakob disease: disease phenotype determined by a DNA polymorphism. *Science* 1992;258:806-8.
- McLean CA, Storey E, Gardner RJM, et al. The D178N (cis-129M) "fatal familial insomnia" mutation associated with diverse clinicopathologic phenotypes in an Australian kindred. *Neurology* 1997;47:1326-8.
- Zerr I, Giese A, Windl O, et al. Phenotypic variability in fatal familial insomnia (D178N-129M) genotype. *Neurology* 1998;51:1398-405.
- Furukawa H, Doh-ura K, Kikuchi H, et al. A comparative study of abnormal prion protein isoforms between Gerstmann-Sträussler-Scheinker syndrome and Creutzfeldt-Jakob disease. *J Neurol Sci* 1998;158:71-5.

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.

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 1996.¹ 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).¹ 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.¹ 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),² motor aphasia, and generalised myoclonus.³ 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 200x10⁶/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.³ 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.⁴ 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.⁵ Tumour necrosis factor has been implicated in neurotoxicity.⁶ 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.³ The observed time to neurological dysfunction after eradication of the parasite and the reported response to steroid treatment³ 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.

A H MOHSEN
M W MCKENDRICK
M L SCHMID
S T GREEN

Department of Infection and Tropical Medicine, Royal Hallamshire Hospital, Sheffield, UK

M HADJIVASSILIOU
Department of Clinical Neurology

C ROMANOWSKI
Department of Neuroradiology

Correspondence to: Dr Abdul H Mohsen, Department of Infection and Tropical Medicine, Royal Hallamshire Hospital, Sheffield S10 2JF, UK Abdul.Mohsen@csuh.nhs.uk

- 1 Mai NTH, Day NPJ, Chuong LV, *et al.* Post-malaria neurological syndrome. *Lancet* 1996;348:917-21.
- 2 De Silva HJ, Gamage R, Herath HKN, *et al.* A delayed onset cerebellar syndrome complicating falciparum malaria. *Ceylon Medical Journal* 1986;31:147-50.
- 3 Schnorf H, Diserens K, Schwyder H, *et al.* Corticosteroid-responsive postmalaria encephalopathy characterised by motor aphasia, myoclonus, and postural tremor. *Arch Neurol* 1998;55:417-20.
- 4 Newton CRJC, Warrell DA. Neurological manifestations of falciparum malaria. *Ann Neurol* 1998;43:695-702.
- 5 De Silva HJ, Hoang P, Dalton H, *et al.* Immune activation during cerebellar dysfunction following *Plasmodium falciparum* malaria. *Trans R Soc Trop Med Hyg* 1992;86:129-31.
- 6 Marks RM, Ward PA, Kunkel SL, *et al.* Tumour necrosis factor induces mRNA for thrombospondin in human endothelial cells. *FASEB J* 1988;2:A1599.

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.¹ 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 hyperintense 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.² 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.³ 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.^{4,5} 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.

LUIS PEDRAZA
MARIO CAMPERO

Department of Neurology, Faculty of Medicine, Universidad de Chile and Laboratory of Clinical Neurophysiology, Clínica Alemana de Santiago, Santiago, Chile

Correspondence to: Dr Luis Pedraza, Unidad de Neurofisiología, Clínica Alemana de Santiago, Avenue Manquehue Norte 1410, 8° piso, Vitacura, Santiago, Chile

- 1 Kimura J. *Electrodiagnosis in diseases of nerve and muscle* (2nd edition). Philadelphia: Davis, 1989:303-31.
- 2 Shahani BT, Young RR. Human orbicularis oculi reflex. *Neurology* 1972;22:149-54.
- 3 Kimura J. Electrically elicited blink reflex in diagnosis of multiple sclerosis. Review of 260 patients over a seven-year period. *Brain* 1975;98:413-426.
- 4 Ishii K, Tamaoka A, Shoji S. Dorsolateral pontine segmental infarction presenting as isolated trigeminal sensory neuropathy. *J Neurol Neurosurg Psychiatry* 1998;65:702.
- 5 Nakamura K, Yamamoto T, Yamashita M. Small medullary infarction presenting as painful trigeminal neuropathy. *J Neurol Neurosurg Psychiatry* 1996;61:138.

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.¹ 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,² 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.¹ However, in higher frontal eyed mammals, levator palpebrae innervation is provided by a single medial