LETTERS

An unusual phenotype of McLeod syndrome with late onset axonal neuropathy

McLeod syndrome is a rare multisystem disorder defined by weak expression of the Kell glycoprotein antigens and the absence of a red blood cell surface antigen, Kx.^{1,2} The gene responsible for McLeod syndrome, *XK*, was cloned in 1994.¹ The *XK* protein contains the Kx antigen missing in patients with McLeod syndrome. Mutation analysis of the *XK* gene has shown different deletions or point mutations in families with this condition.^{2,3}

Clinical features of McLeod syndrome are reported to be heterogeneous.^{2,4,5} Clinical manifestations include acanthocytosis, an increased level of serum creatine kinase (CK), progressive muscular atrophy, seizures, and involuntary movement. As the symptoms and signs of this syndrome seem to be variable even among siblings, it is sometimes difficult to distinguish the condition from other neuromuscular disorders by clinical features and conventional examination.

We report here two cases of McLeod syndrome in brothers and emphasise the variable features of the disease. Phenotypic variability was obvious in the two patients, and one case was unusual because the clinical features greatly resembled an axonal form of Charcot-Marie-Tooth disease.

Case reports

Case 1

A 50 year old man had been complaining of weakness and paraesthesiae in both legs. He first noted weakness in the right leg at the age of 37. Subsequently, the symptom extended to both legs, and he began to be unsteady on his feet. At age 47, he noticed muscular atrophy in his legs. There was no consanguinity in the family. A neurological examination in August 2000 revealed sensorimotor neuropathy with severe weakness and atrophy in both calves and shins (fig 1A). Deep tendon reflexes were diminished in the lower limbs. The ability to sense pinprick and light touch was mildly impaired in the distal parts of the lower extremities. Vibration sense was impaired in both feet. Abnormal involuntary movement was not seen.

Laboratory investigations were unremarkable except for a raised serum CK concentration (1510 IU/L, normal <255). Serum levels of thyroid hormones, vitamin B-12, vitamin E, antinuclear antibody, anti-DNA antibody, and anti-SS-A/SS-B antibodies were normal. In nerve conduction studies, neither compound motor action potentials (CMAP) nor sensory nerve action potentials (SNAP) were elicited in the patient's lower extremities.

Histopathological features of a sural nerve biopsy specimen showed moderate myelinated fibre loss and abundant axonal sprouting in residual myelinated fibres (fig 1B), while onion bulb formation was absent. No apparent amyloid deposits or inflammatory cell infiltrates were seen in the epineurial and endoneurial tissues. An axonal form of Charcot-Marie-Tooth disease was strongly suspected from the clinical features and pathological findings. Although mutation analysis available for the peripheral myelin

protein zero and connexin-32 was done, no mutation was detectable in these genes.

Case 2

A 62 year old man, an elder brother of case 1, was admitted for evaluation of a progressive movement disorder in December 2001. On neurological examination, he had choreic involuntary movement of the extremities, mild weakness in the thighs, and hyporeflexia in all limbs. Pathological reflexes were not elicited, and he showed no sensory disturbance. No personality change or cognitive impairment was seen.

A peripheral blood smear showed acanthocytes in 4% of the red blood cells by May-Giemsa staining. Serum CK was raised to

1710 U/L, with predominant MM isozyme. Brain magnetic resonance imaging showed mild atrophy of the bilateral frontal lobes and caudate nuclei (fig 1C). Nerve conduction studies of the lower limbs suggested mild sensory neuropathy, showing reduced SNAP in the sural nerves (left 2.3 μ V, right 3.6 μ V).

A muscle biopsy specimen taken from the left biceps brachii showed increased variability in fibre diameter. The most striking findings were some scattered necrotic fibres, several basophilic fibres, and an increased number of central nuclei (fig 1D).

An evaluation of Kell antigen expression was subsequently undertaken. Expression of Kell antigens (K2, K4, and K7) on red blood cells was reduced, a result consistent with McLeod syndrome.

Figure 1 (A) Marked amyotrophy of both legs in case 1. (B) Sural nerve specimen obtained from case 1 showing moderate loss of myelinated fibres. Onion bulb formation is not observed. Toluidine blue stained transverse semithin section. Bar = 50 μ . (C) Axial T2 weighted magnetic resonance image of case 2, showing atrophy of the heads of the caudate nuclei. (D) Muscle biopsy specimen obtained from the left biceps brachii of case 2. The specimen shows increased variability of fibre diameter, and a group of basophilic fibres. Bar = 100 μ . (E) Direct DNA sequencing of the *XK* gene. A five base deletion in exon 3 is present at nt position 938 to 942 from the 5' end of the cDNA.

Molecular analysis

After informed consent had been obtained from the brothers, genomic DNA was extracted from peripheral blood by standard procedures. Exons of the *XK* gene were subsequently amplified by polymerase chain reaction as described by Ho *et al.*¹ The analysis showed a five base deletion in exon 3 at nt positions 938 to 942 from the 5' end of the cDNA. This mutation results in a frame shift at codon 286 and the premature stopping of translation at codon 301, as reported previously.² This mutation was found in both cases 1 and 2, whose clinical phenotypes were extremely different.

After mutation analysis of the *XK* gene, we confirmed the presence of acanthocytes in a peripheral blood smear of case 1.

Comment

To date, the clinical features of McLeod syndrome have been reported to be heterogeneous.²⁻⁵ The clinical features and conventional pathological findings in this condition are sometimes difficult to distinguish from other neuromuscular disorders because the expression of symptoms and signs seems to be variable, even among siblings.²⁻⁵ In many cases, chorea, seizures, or muscular atrophy are the most frequently presented symptoms. Daneek *et al* recently reported clinical features of 22 affected patients with mutation analysis of the *XK* gene.² In their investigations, limb chorea—which reflects CNS involvement in McLeod syndrome—was described in all patients. It is extremely difficult to make a diagnosis of this disease where the symptoms and signs are restricted to the peripheral nervous system.

In the present investigation, case 2 was characterised clinically by choreic movement and mild muscular atrophy, frequently seen in the reported cases of McLeod syndrome. In contrast, the symptoms in case 1 were extremely rare. Case 1 showed late onset of symptoms, slowly progressive weakness and amyotrophy of the lower extremities, areflexia, glove and stocking type sensory impairment, an increased level of serum CK, and pathological features with axonal degeneration of the nerve biopsy specimen. He showed no apparent central nervous system involvement 14 years from onset.

Our case 1 was clinically and pathologically indistinguishable from an axonal form of Charcot-Marie-Tooth disease without McLeod serology.

McLeod syndrome should be considered in patients with axonal sensorimotor neuropathy and high CK activity. Abnormal red cell morphology may be a clue to the diagnosis.

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NHS Direct for headache

NHS Direct is a government sponsored, nurse led, telephone helpline available throughout the United Kingdom, offering confidential medical advice without recourse to a doctor by using computerised assessment systems based on clinical algorithms.¹ As algorithms for the management of headache have been formulated, this might be construed as a condition for which NHS Direct would be well suited to offer an appropriate service. Following a protocol used in previous studies of the use of NHS Direct by patients attending neurology outpatient clinics,²⁻⁴ patients with headache were specifically asked about their use of this service.

Of 1000 consecutive unselected patients seen in 118 general neurology outpatient clinics over a period of approximately 10 months by one consultant neurologist, headache was the principal reason for referral or patient complaint during consultation in 208 (21%), a frequency similar to that previously reported by others.⁵ The neurologist's diagnoses, using standard diagnostic criteria,⁶ were: chronic daily headache of tension type (157), drug overuse headache (12), episodic tension type headache (3), and migraine (34); one patient had a cerebral neoplasm, with typical postural features and visual obscurations, and one had coital cephalalgia. Of these 208 patients, 120 (58%) had heard of the NHS Direct telephone helpline. Of these 120 patients, 36 (30%; or 17% of all headache patients) had used the service; only three patients volunteered this information spontaneously. Of the 36 users, in 14 the call to NHS Direct related to headache (39% of NHS Direct users, or 6.7% of all headache patients); two volunteered this information spontaneously. The percentages for awareness and use of NHS Direct in this cohort are similar to those previously reported for an unselected general neurology outpatient clinic surveyed in 2002.³

Of those calling NHS Direct for advice about their headache, five of the 14 reported that they were told to go to hospital or call an ambulance immediately. The neurologist's diagnoses in these five patients were chronic daily headache of tension type in three, episodic tension type headache in one, and migraine without aura in one (in whom the reported NHS Direct diagnosis was cerebral haemorrhage). One patient was told to go to a local NHS walk-in centre (final diagnosis: chronic tension type headache), and another two patients were told to attend their general practitioner (both with chronic tension type headache). NHS Direct diagnosed transient

ischaemic attack in a man thought by the neurologist to have migraine without headache (migraine equivalent). One patient with chronic tension type headache was told to lie in a dark room. One patient phoned for information about side effects of analgesic medication. Three could not recall the outcome of their call to NHS Direct.

Proposals for changes in the primary care of headache in the UK, issued by the British Association for the Study of Headache (BASH), described the role of NHS Direct in headache management as "uncertain," as "algorithms in use cannot provide for the taking of an adequate history to inform advice given."⁷ The current study, although hospital based and reliant on patient report, with all their inherent biases, has provided no evidence to contradict that view. The suggestions emanating from NHS Direct were neither dangerous nor useful. Hence the study does not suggest that NHS Direct can currently replace clinical assessment by a practitioner trained in the diagnosis and management of headache disorders.

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Isolated total tongue paralysis as a manifestation of bilateral medullary infarction

Isolated acute bilateral hypoglossal nerve (CXII) paralysis is a very rare clinical condition which has been described in the context of traumatic mechanical injuries to the nerves.¹ The two nuclei of CXII, located at the tegmentum of the medulla oblongata, are in close proximity and may be damaged at the same time.² However, isolated bilateral CXII paralysis has not been described in cases of medullary infarction. We report a patient presenting with isolated complete tongue paralysis and a small ischaemic area in the medulla affecting both CXII nuclei exclusively.

CASE REPORT

A 49 year old woman with a history of primary biliary cirrhosis presented to the emergency room with acute dysarthria, swallowing difficulty, and inability to protrude her tongue. She was unable to eat, drink, or handle saliva. She denied vertigo, dizziness, nausea, unsteady gait, numbness, or weakness.

Examination showed that she was alert and responsive but was dysarthric and unable to initiate a swallow. Pupils were 3 mm in diameter, equal, and reactive to light and accommodation. Extraocular movements were full. There was no ptosis and the corneal reflex was present bilaterally. Sensation was intact to light touch and pin prick. There was no spontaneous or gaze nystagmus, saccadic pursuit, or ocular dysmetria. Facial symmetry was noted, with no signs of weakness. The gag reflex was present with symmetric palatal elevation. Her tongue had limited protrusion and no side to side movement. The remainder of the cranial nerve examination was normal.

Neuromuscular strength was preserved. There were no sensory deficits to touch, pain, temperature, vibration, or position sense. Deep tendon reflexes were normal and there were no pathological reflexes. Coordination of the extremities was intact. Gait was not ataxic.

Clinical laboratory tests proving normal included an echocardiogram, chest x ray, repetitive nerve stimulation and single fibre electromyography, erythrocyte sedimentation rate, full blood count, serum electrolytes, fasting lipid profile, angiotensin converting enzyme, protein S, protein C, lupus anticoagulant, anticardiolipin antibodies (IgG and IgM), plasma homocysteine levels, C3 and C4 complement, anti-ENA (anti-Sm, SS-A/anti-Ro, SS-B/anti-La, and anti-RNP), antinuclear antibodies, antiacetylcholine antibodies, serum syphilis serology, and cerebrospinal fluid findings. Magnetic resonance imaging (MRI) showed a region of increased signal intensity on T2 weighted and fluid attenuated inversion recovery images, involving only the two CXII nuclei; no further lesions were observed (fig 1). Figure 2 is a schematic drawing of the lesion. Conventional cerebral angiography showed a narrow basilar artery as well as tortuosity of the vertebral artery at the cervical level. The patient required a nasogastric tube for feeding.

Aspirin 300 mg daily was initiated. Four days after the onset of symptoms, the patient began suffering from sustained paroxysmal hiccups. Chlorpromazine 75 mg daily and valproic acid 500 mg daily were then given orally for 10 days, but the hiccups continued. She was then given 5 mg of baclofen orally three times a day, and the hiccups abated within 48 hours. The baclofen was discontinued after one week of treatment, and the hiccups did not recur.

The condition of the patient improved within the following weeks. Two months after onset, she reported the return of some tongue mobility. She began to eat and drink without a nasogastric tube. On examination,

Figure 1 T2 weighted magnetic resonance image at the level of the tegmentum of the upper medulla oblongata, showing hyperintensity confined to the two CXII nuclei.

her tongue had limited ability to protrude but there was some side to side movement. No tongue atrophy was observed. Five months later, she presented with acute diplopia and right facial weakness which lasted for 14 days. Examination showed a right lateral rectus nerve paralysis along with a right peripheral facial nerve paralysis. Further cranial MRI showed no new lesions apart from the previous evidence of brain stem ischaemia. The patient was then switched to warfarin.

A two year follow up examination showed that her tongue mobility had returned to normal. The tongue had full side to side motion and full protrusion. No further strokes occurred and she continues taking warfarin.

COMMENT

Medial medullary infarcts represents less than 0.5% of all cerebral infarcts.^{3,4} They may be unilateral or, rarely, bilateral. The clinical features of bilateral medial medullary infarctions are flaccid quadriplegia sparing the face, bilateral disturbance of deep sensation, weakness of the tongue, and respiratory failure.^{3,4} The case here reported broadens the spectrum of the medial medullary syndrome. The isolated bilateral CXII paralysis in our patient was the only manifestation of a bilateral medullary infarct. Tongue paralysis is caused either by involvement of the fibres of the hypoglossal nerve, which are located just lateral to the medial lemniscus and the pyramid, or by involvement of the nucleus.² The CXII nucleus is placed in the dorsomedial medulla and depends on the territory of the anteromedial arteries, which, in addition, supply the medial portion of the pyramidal tract and its decussation, the medial lemniscus, and the medial longitudinal fasciculus. The anteromedial arteries usually arise from the anterior spinal artery to the caudal medulla and from the distal vertebral artery or proximal basilar artery to the rostral medulla.^{3,4}

With regard to aetiology, the vertebrobasilar system was found to be hypoplastic. We feel that an anomalous branch of a vertebral

Figure 2 Schematic drawing of the lesion at the mid-medullary level. The shadowed area indicates the lesion.

artery supplied both sides of medial medullary area. Distal occlusion of this rostral branch at the level of the dorsal medulla resulted in a restricted bilateral CXII infarct. Our patient had a further vertebrobasilar stroke and was switched to warfarin. Patients with ischaemia in the territory of a hypoplastic vertebrobasilar system may be treated with either antiplatelet agents or warfarin.⁵ However, recurrent transient ischaemic attacks may be more common in patients given antiplatelet agents. In a recent series, for example, two of four patients with symptomatic vertebrobasilar hypoplasia who were initially treated with an antiplatelet agent developed recurrent transient ischaemic attacks. In contrast, none of the patients treated with warfarin had recurrent symptoms.⁵

In conclusion, this case shows that an isolated complete tongue paralysis can be produced by bilateral medullary infarction, a finding that broadens our understanding of the spectrum of medial medullary syndrome.

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