CASE REPORT

The first report of a Chinese family with McLeod syndrome

Bik Ling Man,¹ Yuet Ping Yuen,² Yat Pang Fu¹

¹Department of Medicine and Geriatrics, Tuen Mun Hospital, Hong Kong, Hong Kong
²Department of Chemical Pathology, Prince of Wales Hospital, the Chinese University of Hong Kong, Hong Kong, Hong Kong

Correspondence to
 Dr Bik Ling Man,
 beli_man@yahoo.com

Accepted 4 May 2014

SUMMARY

We report the first case of a Chinese family with McLeod syndrome (MLS). The two affected brothers show significant phenotypic heterogeneity. The index case has peripheral acanthocytosis, choreoathetosis of his feet, a slowly progressive neuropathy and myopathy, and an elevated serum creatine kinase (CK) level. His elder brother has more prominent chorea of the shoulders, epilepsy, a rapidly progressive neuropathy and normal serum CK. The diagnosis of MLS was confirmed by a genetic test which showed a hemizygous frameshift mutation in the XK gene.

BACKGROUND

McLeod syndrome (MLS) is a rare X linked recessive multisystem disorder which was first found in the blood donor Hugh McLeod in 1961.¹ Despite its recognition in the medical literature, the syndrome is rarely described in Chinese people due to a low index of suspicion by clinicians and lack of confirmatory tests. We reported the first case of MLS in the Chinese in this journal.² The elder brother of the index case was later found to have the same mutation in the XK gene. These two brothers exhibit much phenotypic heterogeneity.

CASE PRESENTATION

Case 1 (index case)

The clinical findings of the index case have been reported previously.² In brief, the patient was a 47-year-old Chinese man who presented with progressive wasting of limb muscles over a few years. He also had bilateral genu varus, hypoaesthesia of fingers and toes to pain, and involuntary movement of his legs. His gait was waddling and he had multiple falls in the past few years. The examination revealed wasting of bilateral temporal, left shoulder, left thigh and bilateral hand muscles. The jerks were hyporeflexic and there was choreoathetosis of his feet. Laboratory testing was significant for an elevation of serum creatine kinase (CK) level at 2148 U/L (normal 62–279). Brain MRI showed atrophy of basal ganglion and generalised brain atrophy. Nerve conduction study showed sensorimotor axonal polyneuropathy. Electromyography (EMG) revealed combined neurogenic and myopathic changes. Muscle biopsy confirmed myopathic changes. ECG and echocardiography were normal. Blood smear showed acanthocytosis. Kell blood group testing showed weak expression of Kell red blood cell (RBC) antigens and absent Kx RBC antigens. Sequence analysis of the XK gene detected a hemizygous mutation c.856_860delCTCTA (reference

sequence NM_021083.2). The patient's condition was stable and he was able to walk with a stick. The choreoathetosis of his feet was mild and did not need any treatment.

Case 2

A 53-year-old man, the elder brother of the index case, suffered from epilepsy ever since he was 39 years old. He developed progressive wasting of limb muscles and involuntary movements of shoulders from age 40. His disability increased rapidly and he became bedridden after a few years. He also had recurrent episodes of suppurative inflammations of the spine, psoas muscles, knee, shoulders, elbow and buttock which required multiple surgical drainages. Physical examination showed wasting of temporalis, distal hand and leg muscles. The jerks were hyporeflexic and there was chorea of his shoulders (video 1). The serum CK level was normal. Brain MRI showed mild atrophy of bilateral caudate nucleus with mild bilateral T2-weighted hyperintensities in putamen (figure 1). Nerve conduction study showed sensorimotor axonal polyneuropathy. EMG revealed chronic neurogenic changes and no evidence of myopathy. Sequence analysis showed the same XK mutation as in his brother. Sequence analysis of the CYBB gene for X linked chronic granulomatous disease (CGD) was negative. His seizure was controlled by phenytoin 360 mg daily and valproate 400 mg twice daily. He did not need any specific treatment for the chorea. He was dependent for his activities of daily living and required caring in an old age home.

The eldest brother of these patients was asymptomatic and his test for the XK gene was normal. The elder sister was not available for genetic testing and she was reported to be asymptomatic. Regular follow-up in the neurology clinic with annual echocardiogram and Holter screening were offered to the two patients.

Video 1 Chorea of Shoulders.

CrossMark

To cite: Man BL, Yuen YP, Fu YP. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-202785

Figure 1 MRI T2-weighted (T2W) image showing mild atrophy of bilateral caudate nucleus with mild T2W hyperintensities in putamen (arrow).

DISCUSSION

MLS is an X linked multisystem disorder with haematological, neuromuscular and central nervous system (CNS) involvement.^{3 4} MLS is a subtype of neuroacanthocytosis which is characterised by the absence of Kx RBC antigens, weak expression of Kell RBC antigens, acanthocytosis and compensated haemolysis.⁴ Patients may develop neurological signs and symptoms with a mean onset age from 30 to 40 years, and high penetrance of the disorder.³ Neuromuscular manifestations include myopathy, sensorimotor axonal neuropathy and cardiomyopathy. CNS manifestations consist of a choreic movement disorder, 'subcortical' neurobehavioural deficits, psychiatric abnormalities and generalised seizures.^{3 4} Most MLS patients have an elevated serum CK level but this is not a consistent finding.⁵ Our second patient had a normal CK level and EMG findings of chronic neurogenic changes with no evidence of myopathy. The differential diagnoses of MLS include chorea acanthocytosis, Huntington's disease-like 2 and pantothenate kinase-associated neurodegeneration. The diagnosis is confirmed by molecular testing.

MLS is caused by mutations of the XK gene encoding the XK protein, which carries the Kx RBC antigen.⁶ A hemizygous XK mutation c.856_860delCTCTA was detected in our patients. This mutation has been reported previously in patients affected by MLS.³ The 5-nucleotide deletion is predicted to create a premature stop codon at amino position 301 (p.Leu286Tyrfs*16). Although the exact function of the human XK protein is not yet known, available data suggest an important role for apoptosis regulation.⁴ There is no clear-cut genotype–phenotype correlation and phenotypic heterogeneity is common among affected

family members.^{7 8} Our index patient had mild symptoms and a slowly progressive disease. His elder brother had a much more severe disease and became bedridden a few years after disease onset. One peculiar feature of this patient was that he had recurrent episodes of suppurative inflammations, which was suggestive of CGD. The X linked form of CGD is caused by mutations in the *CYBB* gene mapped to the Xp21.1 region.⁹ Large deletions that extend across multiple genes in the short arm of the X chromosome will result in 'contiguous gene deletion syndrome', which encompasses MLS, X linked CGD, Duchenne muscular dystrophy and X linked retinitis pigmentosa.⁹ If the elder brother was the proband who came first for clinical investigation, the most probable diagnosis would be contiguous gene deletion syndrome that involved the *XK* and *CYBB* genes. However, this possibility was refuted by our DNA analysis.

Learning points

- ▶ We report the first case of a Chinese family with McLeod syndrome.
- ▶ Phenotypic heterogeneity is common among family members with McLeod syndrome.
- ▶ Serum creatine kinase can be normal in McLeod syndrome.
- ▶ McLeod syndrome may be associated with other X linked disorders such as X linked chronic granulomatous disease, Duchenne muscular dystrophy and X linked retinitis pigmentosa.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Allen FH Jr, Krabbe SM, Corcoran PA. A new phenotype (McLeod) in the Kell blood-group system. *Vox Sang* 1961;6:555–60.
- 2 Man BL, Yuen YP, Yip SF, *et al*. The first case report of McLeod syndrome in a Chinese patient. *BMJ Case Rep* 2013;2013:pil:bcr2013200205.
- 3 Danek A, Rubio JP, Rampoldi L, *et al*. McLeod neuroacanthocytosis: genotype and phenotype. *Ann Neurol* 2001;50:755–64.
- 4 Jung HH, Danek A, Frey BM. McLeod syndrome: a neurohaematological disorder. *Vox Sang* 2007;93:112–21.
- 5 Marsh WL. Chronic granulomatous disease, the McLeod syndrome, and the Kell blood groups. *Birth Defects Orig Artic Ser* 1978;14:9–25.
- 6 Ho M, Chelly J, Carter N, *et al*. Isolation of the gene for McLeod syndrome that encodes a novel membrane transport protein. *Cell* 1994;77:869–80.
- 7 Chakravarty A, Bhattacharya P, Banerjee D, *et al*. McLeod syndrome: report of an Indian family with phenotypic heterogeneity. *Ann Indian Acad Neurol* 2011;14:144.
- 8 Walker RH, Jung HH, Tison F, *et al*. Phenotypic variation among brothers with the McLeod neuroacanthocytosis syndrome. *Mov Disord* 2007;22:244–8.
- 9 Watkins CE, Litchfield J, Song E, *et al*. Chronic granulomatous disease, the McLeod phenotype and the contiguous gene deletion syndrome—a review. *Clin Mol Allergy* 2011;9:13.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow