Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Very Long Time Persistent HyperCKemia as the First Manifestation of McLeod Syndrome: A Case Report

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McLeod syndrome (MLS) is a very rare genetic X-linked condition due to *XK* gene mutations and characterized by the development of chorea, psychiatric and cognitive impairment, seizures, cardiomyopathy, muscular involvement and the presence of acanthocytes.[1]

We present the case of a patient with very long lasting mild myalgia and elevated creatine kinase (CK) who developed late-onset chorea and was finally diagnosed with MLS.

Case Report

This is a 61-year-old man with a 20-year history of mild myalgia and elevated CK, with values ranging from 600 to 3,000 IU/L. Electromyography showed the presence of isolated polyphasic potentials of reduced amplitude in both quadriceps. Muscle biopsy revealed mild myopathic changes. The routine clinical approach in paucisymptomatic hyperCKemia including dried blood spot for Pompe disease, ischemic forearm test and carnitine profiles, showed normal results. Whole-body muscle MRI performed more recently, showed severe fatty infiltration in several leg muscles (Fig. 1C). He was referred to our neurology outpatient clinics because of the presence of generalized involuntary movements, which had increased slightly in severity over time but without interfering with his daily life activities. In fact, he is still working as a carpenter.

Past history was relevant for an only episode of generalized seizure that he suffered at the age of 55. Electroencephalogram recording was normal. Family history disclosed that his younger brother had been diagnosed with epilepsy since childhood and died suddenly at the age of 43, while his older brother, diagnosed with schizophrenia, also died suddenly at the age of 45.

At examination he showed slight but frequent choreatic movements on the lips, face, trunk, and limbs, involving mainly both feet (Video 1). Impaired ocular saccadic movements, tongue impersistence, slight dysarthria, slight bradykinesia and unsteadiness in the tandem walking were also present. The total motor score of the Unified Huntington's Disease Rating (HD) Scale was 20. There was not muscle weakness. The osteotendinous reflexes were absent. No significant cognitive or psychiatric alterations were detected on neuropsychological assessment.

Brain MRI revealed bilateral atrophy of caudate nuclei (Fig. 1A,B) and genetic testing ruled out HD. Considering the relevance of chorea together with the persistent elevated CK, a peripheral blood smear was performed demonstrating the presence of abundant acanthocytes. The immunohematology study detected a weak expression of Kell system antigens, and the patient's red blood cells did not react with antibodies anti-Kx. Genetic study demonstrated the presence of a *nonsense* mutation (c.397C>T) at exon 2 of *XK* gene leading to a premature stop codon (p.Arg133Ter). Cardiac holter monitoring was normal but cardiac MRI revealed mild left ventricle hypertrophy (septum 14 mm; lateral wall 12 mm) (Fig. 1D), mild dilated cardiomyopathy, and reduced cardiac ejection fraction (40%).

Discussion

McLeod syndrome together with chorea-acanthocytosis (VPS13A disease)[1] constitute the core of the neuroacanthocytosis syndromes. They not only share an HD-like phenotype but probably also common pathogenic mechanisms related to

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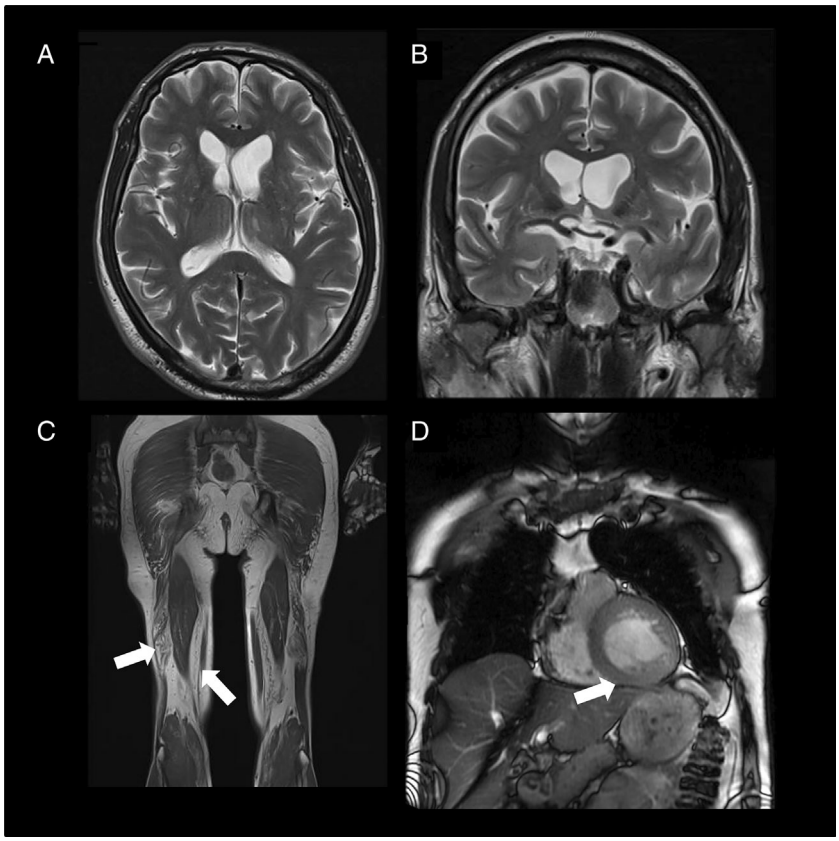

FIG 1. (A, B) Brain MRI on t2-weighted sequences showing moderate atrophy of both caudate nuclei with constitutional asymmetry between both ventricular horns. (C) Muscle MRI on t1-tse sequences showing severe fatty infiltration of semimembranosus and biceps femoris muscles (arrows) in both legs. (D) Cardiac MRI on FIESTA sequences showing moderate hypertrophy (12 mm) of the left ventricle lateral wall (arrow).

dysregulation of VPS13A-XK complex interaction.[2,3] The main features distinguishing MLS from VPS13A disease are X-linked inheritance, older age at onset, erythrocyte immunophenotype and more frequent and severe cardiac involvement.[4]

At least 29 different mutations at *XK* have been identified.[5] The mutation c.397C>T found in our patient lead to a truncated protein of 132 amino acids. Several cases with the p.R133X (p.Arg133Ter) mutation have previously been reported.[3,6–9] The initial symptoms of mutation carriers usually consist of psychiatric alterations and/or chorea (Table 1). The age at onset is variable, ranging from 30 to 65. HyperCKemia and caudate atrophy on the MRI were reported in all patients but one. Compared to the patients described, our case stands out for the isolated long lasting mild muscle involvement associated to very late onset chorea and the absence of psychiatric and cognitive symptoms so far.

The absence of neuropsychiatric illness in our patient is somehow discrepant from the usual finding in MLS, in which schizophrenia-like psychosis, obsessive–compulsive disorder, dysexecutive syndromes, and depression are common symptoms.[4] On the other hand, the history of schizophrenia in one of his brothers, points out the possibility of intrafamilial phenotype variability in MLS.[10]

Cardiac involvement has been reported in about 60% of patients and is considered the main cause of sudden death in MLS.[4] Our patient was diagnosed with dilated cardiomyopathy and his brothers, suspected of being affected by the disease, died suddenly suggesting also possible heart damage.

McLeod syndrome diagnosis is challenging due to the disease rarity and its phenotypic variability. MLS should be considered in male patients with chorea and psychiatric symptoms after exclusion of other choreas, mainly HD. Diagnostic keys should be the presence of cardiomyopathy and muscle involvement with elevated CK levels associated to a HD-like phenotype. However, our case raises the question to consider MLS by specialized neuromuscular units in patients with isolated long lasting hyperCKemia of unknown etiology even in absence of other clinical features such as chorea, psychiatric symptoms or cardiomyopathy.

Video 1. This video shows slight generalized choreic movements, involving mainly lips and feet, and shoulder shrugging.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13502

TABLE 1 *Clinical features of McLeod patients with the c.397C>T (p.Arg133Ter) mutation*

Case	Age at onset	Age at sample	Initial symptom	Psychiatric or cognitive symptom	Acanthocytes	Seizures	Tendon reflexes	CK	Cardiomyopathy
1[8]	58	61	Depression	Depression	+	+	−	Increased	UK
2[6]	42	14	Chorea	Depression, anxiety, OCD	+	−	−	Increased	−
3[7]	30	32	Behavioral changes, Chorea	Irritability	+	−	+	Increased	UK
4[9]	45	51	Irritability, Chorea	Irritability, aggression	−	−	+	UK	+
5[3]	65	50	Chorea	Cognitive decline	+	−	UK	Increased	UK

Abbreviations: OCD, obsessive–compulsive disorder; UK, unknown.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

VT: 1B, 1C, 3A, 3B;
CP: 1B, 3B;
PS: 1B, 3B;
AS: 1B, 1C, 3B;
CS: 1B, 1C, 3B;
JMG: 1B, 1C, 3B;
EM: 1A, 1B, 1C, 3B.

Disclosures

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