Clinical Neurology and Neurosurgery 184 (2019) 105421

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Case Report

The first case report of McLeod syndrome in an infant with a novel mutation (c.89C > A, p. Ser30X) in *XK*

Pei-Chao Tian*, Yue Wang, Zheng Chen, Dan-Dan Shi, Huai-li Wang, Qiang Luo

Department of Pediatrics, First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

ARTICLE INFO

Keywords:
McLeod syndrome
Infant
Creatine
Kinase
XK
Nonsense mutation

ABSTRACT

McLeod syndrome (MLS) is a rare multisystem disorder and X-linked recessive inheritance disorder caused by mutations of the X-linked Kx blood group (XK) gene. The manifestations progress slowly and mainly appear in middle age, which make it difficult to distinguish MLS from other neuromuscular disorders. Here, we present a case of a 10-month-old Chinese boy who was taken to hospital for herpes of the extremities and oral cavity along with febrile seizures in June 2017. The laboratory test revealed persistent elevated levels of serum creatine phosphokinase and abnormal liver function. The results of the electrocardiogram showed sinus tachycardia, and magnetic resonance imaging of the brain showed enlarged bilateral ventricles and third ventricle. Genetic analysis by next-generation sequencing revealed a novel nonsense mutation c.89C > A (p. Ser30X) in exon 1 of XK. To the best of our knowledge, this is the first case report of infants with MLS confirmed by genetic analysis.

1. Introduction

McLeod syndrome (MLS) is a rare multisystem and X-linked recessive inheritance disorder caused by mutations in the *X-linked Kx blood group* (*XK*) gene. Patients with MLS are characterized by the absence of the Kx red blood cell (RBC) antigen, weak expression of Kell RBC antigens, acanthocytosis, compensated hemolysis, and elevated serum creatine kinase (CK) levels. The onset age of neurological symptoms ranges between 20 and 60 years, and the manifestations vary widely and progress slowly. Among them, neuromuscular manifestations include myopathy, sensory-motor axonal neuropathy and cardiomyopathy, and the central nervous system (CNS) manifestations consist of a choreatic movement disorder, 'subcortical' neurobehavioral deficits, psychiatric abnormalities and generalized seizures. Some patients also exhibit varying degrees of cardiologic manifestations [1]. Here, we present a case of a Chinese infant patient diagnosed with MLS by next-generation sequencing (NGS). A novel nonsense mutation c.89C > A (p. Ser30X) in exon 1 of *XK* was detected. This report is the first case of MLS diagnosed in an infant.

2. Cases report

The patient, a 10-month-old Chinese boy, was taken to the hospital because of herpes affecting the extremities and mouth in addition to febrile seizures. There were no obvious abnormalities in the development of the patient. At birth, the boy was G2P2 with weight of 3.5 kg; his birth history included repeatedly increased serum enzyme levels and congenital cardiac dysfunction (the specific condition is not clear). His parents and elder sister were healthy, and there was no additional family history of genetic diseases.

A laboratory test revealed persistently elevated serum CK and abnormal liver function (Supplementary Table 1). The serum CK, aspartate aminotransferase (ALT) and alkaline phosphatase (AST) levels reached 14889 U/L, 449 U/L and 348 U/L, respectively. The serum levels of CK-MB, lactic dehydrogenase and hydroxybutyrate dehydrogenase were also abnormal. Hepatitis e antibody was found to be positive. Laboratory tests showed that his myoglobin and troponin levels reached 368.3 ng/ml and 63.4 pg/ml, respectively. Peripheral blood smears revealed no acanthocytosis or other hematologic abnormalities. The electrocardiogram showed sinus tachycardia, a type of dysrhythmia. The magnetic resonance imaging of the brain showed enlarged bilateral ventricles and third ventricle (Fig. 1a, b). The results of the ultrasounds of the liver, pancreas and spleen were normal.

NGS with exome sequencing of a panel and Sanger sequencing were conducted by Wuhan Kindstar Diagnostics Co., Ltd. (Wuhan, China) according to standard procedures after receiving informed consent. The panel contains 431 selected genes that are reported to cause neuromuscular disease. The NGS results showed a novel nonsense mutation c.89C > A (p. Ser30X) in exon 1 of *XK* (Fig. 1c). The same mutation was found in his healthy mother and elder sister by Sanger sequencing

* Corresponding author at: Department of Pediatrics, First Affiliated Hospital of Zhengzhou University, Zhengzhou, 450052, China.
E-mail address: tpczzu@126.com (P.-C. Tian).

https://doi.org/10.1016/j.clineuro.2019.105421
Received 17 May 2018; Received in revised form 1 July 2019; Accepted 7 July 2019
Available online 12 July 2019
0303-8467/

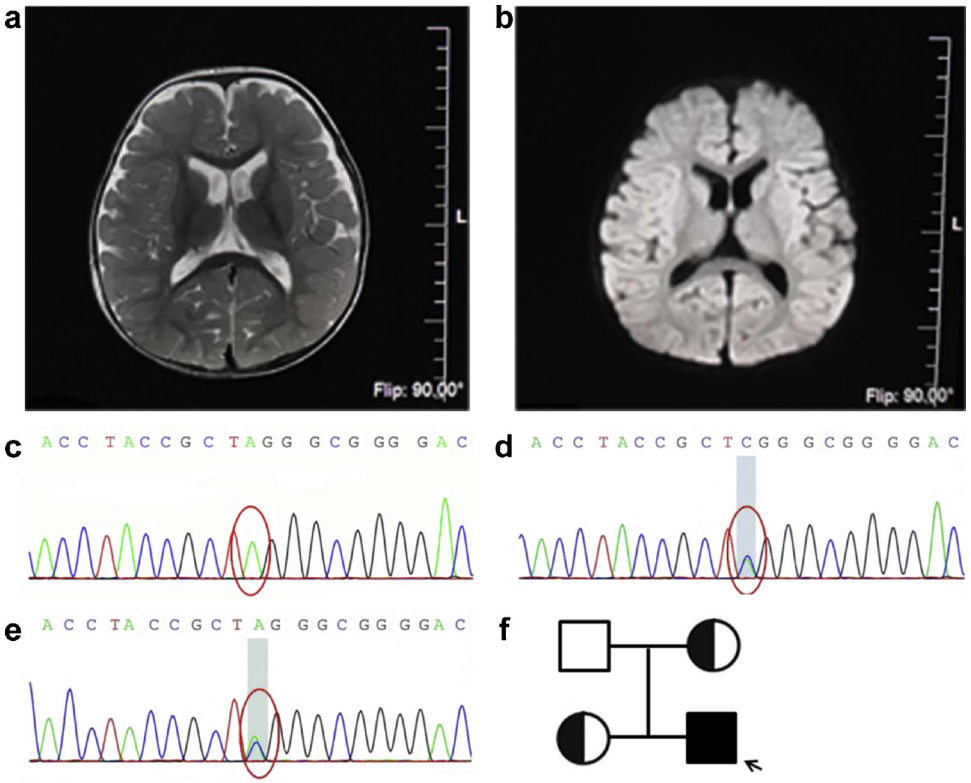

Fig. 1. Brain MRI, the results of DNA sequencing and pedigree of the family of the patient. In this figure, a and b show that the patient had no obvious abnormalities on MRI of the brain. The patient (c) was found to be a hemizygote for a maternally inherited (d) c.89C > A mutation. His elder sister (e) was found to be a heterozygous mutation carrier with normal clinical presentation. The black square (arrow plot) denotes the patient with both clinical manifestations of MLS and a genetic mutation in *XK* (f). The mother and elder sister were carriers who carried the same mutation of *XK* without typical symptoms of MLS.

(Fig. 1d, e). To date, this mutation has not been previously reported in public databases, such as PubMed, the Human Gene Mutation Database (HGMD) and the Exome Variant Server. This nonsense mutation (p. Ser30X) would result in a truncation of the XK protein (containing 29 amino acids), which could lead to disease.

3. Discussion

The McLeod phenotype is defined by a weakened expression of antigens in the Kell blood group system, the absence of Kx antigens and acanthocytosis [1]. The Kx antigen was not detected due to limited resources. The laboratory test results for this 10-month-old patient showed no acanthocytosis or other hematologic abnormalities. Thus, we are not sure whether the boy is too young for the different hematological manifestations. This needs to be clarified by more case reports and may be helpful for the early diagnosis of MLS.

MLS is a multisystem disorder with hematological, neuromuscular and CNS involvement. In addition to acanthocytosis, most patients with MLS also show elevated serum CK levels and tend to develop severe neurological disorders [1]. In this case, the serum levels of CK and biochemical markers of liver function, such as ALT and AST, are persistently elevated. Moreover, there were no remarkable abnormalities in terms of neurological symptoms in the boy. These features in this patient are not consistent with those in reported adult patients. This is probably because the patients reported previously were between 20 and 60 years old, most of whom were diagnosed after the onset of neurological manifestations [2,3]. We speculate that the boy may be in the pre-neurologic stage of MLS because he is only 10 months old. It is impossible to predict whether neurological symptoms will appear and worsen with age.

A recent report showed that a 57-year-old man with a novel *XK* mutation, c.642 G > A (p. Trp214X), was diagnosed with MLS after receiving a heart transplant [4]. In this case, a 10-month-old boy was born with congenital cardiac dysfunction. The electrocardiography showed sinus tachycardia. Therefore, cardiac abnormalities may be present regardless of the age of MLS patients.

The genetic test for *XK* mutations is considered to be the gold standard in the diagnosis of MLS [5]. By January 2018, 39 mutations of *XK* had been recorded in the HGMD. In this case, the patient was too young and had no obvious neurological abnormalities, which resulted in a difficulty in diagnosis given the common clinical features. NGS technology combined with Sanger sequencing was used for the comprehensive screening of human hereditary pathogenic genes in the patient. Finally, a novel c.89C > A mutation in *XK* was detected, and the patient was diagnosed with MLS. This mutation leads to an early stop codon, resulting in the truncation of the XK protein. Thus, the c.89C > A mutation of *XK* was speculated to be a disease-causing mutation.

4. Conclusion

The discovery of this novel c.89C > A mutation enriches the known mutation spectrum in *XK*, and the result of genetic testing could provide important evidence and guidance for early diagnosis and treatment in this 10-month-old Chinese boy with MLS.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2019.105421.

References

[1] E. Roulis, C. Hyland, R. Flower, et al., Molecular basis and clinical overview of McLeod syndrome compared with other neuroacanthocytosis syndromes a review, JAMA Neurol. 75 (2018) 1554–1562.
[2] H.H. Jung, A. Danek, R.H. Walker, Neuroacanthocytosis syndromes, Orphanet J. Rare Dis. 6 (1) (2011) 68.
[3] H.H. Jung, M. Hergersberg, S. Kneifel, et al., McLeod syndrome: a novel mutation, predominant psychiatric manifestations, and distinct striatal imaging findings, Ann. Neurol. 49 (2001) 384–392.
[4] C. Laurencin, L. Sebbag, G. Jousserand, et al., Novel XK mutation in a McLeod patient diagnosed after heart transplant, Clin. Neurol. Neurosurg 168 (2018) 64.
[5] B.L. Man, Y.P. Yuen, S.F. Yip, et al., The first case report of McLeod syndrome in a Chinese patient, BMJ Case Rep. 2013 (2013) bcr2013200205.