SCIE DOI: 10.14744/scie.2023.79745
South. Clin. Ist. Euras. 2023;34(4):371-373

Case Report

McLeod Syndrome – A Rare Seen Chorea Etiology with Different Mutations

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Submitted: 02.12.2022
Revised: 14.12.2022
Accepted: 16.07.2023

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Keywords: Chorea; Mcleod syndrome; neuroachantocytosis; novel mutation; point mutation; XK gene.

ABSTRACT

McLeod syndrome is a rare seen chorea etiology. A patient with chorea, epilepsy and cardiac problems usually suggests a neuroachantocytosis syndrome and the definite diagnosis depends on a detailed genetic investigation. Here we report 57 and 39 years old males who developed choreiform movements and tics afterwards, causing social disturbances and walking difficulty. Depending on the acanthocytosis seen on peripheral blood smear and genetic investigation, the patients has been diagnosed as McLeod syndrome with a novel and point mutations.

INTRODUCTION

Neuroacanthocytosis (NA) is a heterogeneous group of hereditary syndromes characterized by the association of neurological abnormalities with acanthocytosis. It consists of a group of genetic diseases associated with the degeneration of the basal ganglia. The prevalence is between one and five in one million for each disease. The rate of acanthocytosis varies among diseases and can be demonstrated by peripheral smear investigations.[1] Acanthocytosis is divided into three groups: Core NA syndrome, NA with lipoprotein disorders, and acanthocytosis in systemic diseases where neurological findings may also be present. Core NA syndromes that are commonly accompanied by movement disorders are chorea-acanthocytosis, X-linked McLeod syndrome (MLS), neurodegeneration with brain iron accumulation, and Huntington disease-like-2 (HDL2). These four syndromes are differentiated from each other depending on clinical and laboratory findings, but the cases are definitely diagnosed depending on genetic investigation.[2] We report two cases of MLS presenting with generalized chorea, tics, and epilepsy.

Case 1

A 57-year-old male consulted us from an epilepsy outpatient clinic with complaints of tic-like kissing movements on the face and involuntary movements in the arms, legs, and tongue. The involuntary movements were diagnosed as chorea. The severity of the choreiform movements was causing an imbalance during walking. All these movements had been present for about 12 years but had increased

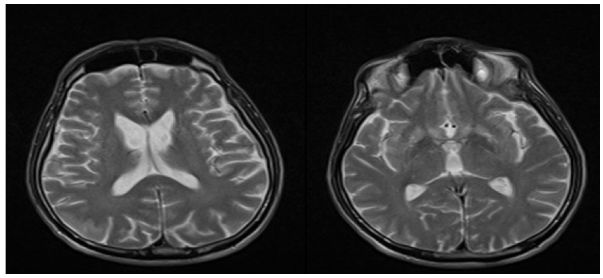

Figure 1. MRI show that putamen and caudat body atrophy.

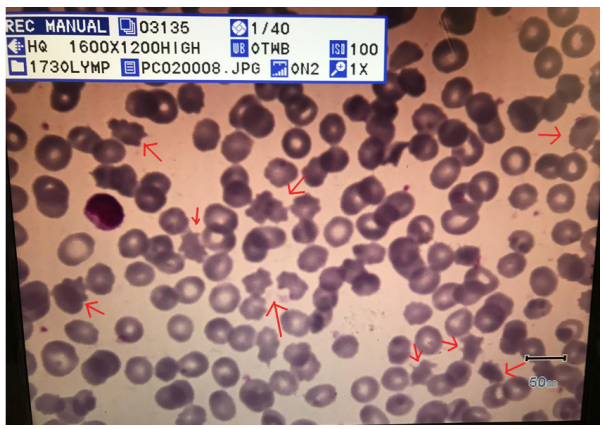

Figure 2. Acanthocytosis in blood smear. Peripheral blood; Wright Stain; ×100 magnification; smear showed frequent acanthocytes.

in the past 5 years. He had a history of epilepsy, which was diagnosed 14 years ago. He was having tonic-clonic generalized seizures, which were under control with levetiracetam treatment. His neurological examination was normal, except for hypoactive deep tendon reflexes and involuntary movements compatible with chorea affecting his face and distal extremities. He had prominent obsessions and anxiety. There was no similar disease history in his family. Laboratory testing was significant for an elevation in a serum creatinine kinase (CK) level of 2148 U/L (normal 62–279). Serum glucose, electrolyte, Vitamin B12, kidney and liver function tests, and the other blood tests were normal. Tumor markers, celiac antibodies, and ELISA antibody were found to be negative. His electroencephalogram (EEG) was normal. An electromyography test was performed, pointing out mild carpal tunnel syndrome and ulnar nerve entrapment on the left side. Magnetic resonance imaging (MRI) of the brain showed atrophy of the basal ganglion and mild generalized brain atrophy (Fig. 1). A peripheral blood smear examination was performed. Acanthocytes were observed in at least 30% of erythrocytes with normochromic normocytic structure (Fig. 2). When evaluated morphologically, the present smear findings were found to be significant for NA. As a result of the laboratory evaluation, a genetic test was sent from the patient with a pre-diagnosis of NA for subgroup examination. Genetic analysis was performed using whole-exome sequencing and bioinformatic analysis method and a novel mutation (p.Leu286TyrfsTer16) (c.854_858delCTCTA) in the XK gene was observed as homozygous in the XK gene, which is compatible with MLS. Since MLS is related to cardiac abnormalities, we referred the patient to a cardiologist. The electrocardiogram and echocardiography were interpreted as normal, but follow-up was recommended for the patient. Tetrabenazine was started for the choreiform movements, and a marked decrease in his choreiform movements was observed.

Case 2

A 39-year-old male patient presented with tic-like kissing movements on the face and involuntary choreiform movements in the arms and legs. In addition, complaints of biting on the lips, the desire to move forward in the tongue, and involuntary noise in the form of throat clearing started. All these movements had been present for about 35 years but had increased in the past 2 years. The patient was diagnosed with chorea in another clinic and tetrabenazine treatment was started. The patient was hospitalized by a psychiatrist due to excessive spending, aggression, depressive mood, obsessions, and suicide attempts 2–3 years before the neurological complaints started, and valproate and clozapine were started with the diagnosis of bipolar affective disorder and obsessive-compulsive disorder. The patient had generalized epileptic seizures 2 years ago. Levetiracetam treatment was started. He also had heart failure and arrhythmia. His older brother had similar involuntary movements in his family history. However, it was reported that he died at the age of fifty. In his neurological examination, there was also dysarthric speech, difficulty swallowing, and tongue protrusion. Extremity distals were atrophic, and hypoactive deep tendon reflexes were present. Laboratory testing was significant for an elevation in a serum CK level of 4536 U/L (normal 62–279). An MRI of the brain showed atrophy of the basal ganglion and mild generalized brain atrophy. In EEG, generalized and frequently recurring sharp-slow wave activity was detected. Sensory-motor axonal neuropathy was detected in nerve conduction study. Acanthocytes were observed in at least 21% of erythrocytes with normochrome normocyte structure. Genetic analysis was performed using the whole-exome sequencing and bioinformatic analysis methods and sequencing analysis of the XK gene: A point mutation of c.397 C>T= (thymine instead of cytosine) mutation was detected in exon 2. The patient was diagnosed with MLS. The tetrabenazine dose was reduced because the patient had a depressive mood. There was no clinical worsening of choreiform movements. 15 IU of botulinum toxin was applied to the genioglossus muscle and 10 IU to the tongue muscle due to swallowing disorders and tongue protrusion. Protrusion was partially reduced.

DISCUSSION

MLS is an X-linked inherited disease associated with poor expression of the blood group antigens Kx and Kell anti-

gens. The onset of neurological symptoms varies between 25 and 60 years.[3] The duration of the illness can usually be more than 30 years. Its clinical features include chorea, facial dyskinesias, and vocalizations. Our patients had facial tic-like kissing movements, which made the case interesting at first sight and also generalized chorea was an evident finding. Tic-like movements are commonly seen in the neurodegenerative diseases HDL and NA.[4] Psychiatric symptoms, including depression, schizophrenia-like psychosis, and obsessive-compulsive disorder, are common in MLS, as seen in our patients.[5] Generalized seizures can be observed in half of the MLS patients. High CK levels are almost always found. Approximately half of the patients develop muscle weakness and atrophy. Cardiomyopathy is seen in 60% of MLS patients. There may be malignant arrhythmia or dilated cardiomyopathy manifested by atrial fibrillation.[1-3] Cardiac complications are common causes of death. Therefore, a cardiologic evaluation should always be performed in MLS patients and asymptomatic carriers of the McLeod blood group. In our cases, facial dyskinesia and tic disorders, anxiety and obsession, and choreiform movements involving extremities, hyporeflexia, and epileptiform seizures mostly suggested chorea-acanthocytosis and MLS. The most important difference between these two syndromes is cardiac involvement which is commonly related to MLS. However, our first patient's cardiac examination did not reveal any pathology; our second patient had dysrhythmia and heart failure. Cardiac abnormalities of MLS patients were examined in a study by Oechslin et al.[6] In this study, one of the patients also did not show any cardiac abnormalities. Neuroradiologically, there is progressive striatal atrophy, especially affecting the head of the caudate nucleus, in MLS patients, as in our patients.[7] Gene deletions, insertions, and point mutations that affect RNA splicing or that lead to premature stop codons have been reported to cause the McLeod phenotype. The McLeod phenotype may also be caused by mutations at a different splice site and by a novel mutation encoding an amino acid substitution that prevents transport to the cell surface. When we investigated the literature, we found that 39 mutations and 17 large-scale deletions had been identified in MLS patients in a review written by Roulis et al.[8]

Conclusion

In our first patient's genetic investigation, a novel mutation has been described after whole-exome analysis. In our second case, a point mutation was detected. While there was no cardiac involvement in the first of our cases, we think that the presence of cardiac involvement in our second case may be due to different mutation types and molecular defects.

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: B.Ö.B., F.G.Ş.; Design: F.G.Ş., B.E.D.; Supervision: B.Ö.B., F.G.Ş.; Fundings: İ.G.A., A.Ç., F.G.Ş.; Materials: A.Ç., B.E.D.; Data: İ.G.A., A.Ç., F.G.Ş.; Analysis: B.Ö.B., F.G.Ş.; Literature search: F.G.Ş., İ.G.A.; Writing: F.G.Ş., B.E.D.; Critical revision: B.Ö.B., F.G.Ş.

Conflict of Interest

None declared.

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McLeod Sendromu; Farklı Mutasyonlara Sahip Nadir Görülen Bir Kore Nedeni

McLeod sendromu koreye sebep olan nadir görülen bir hastalıktır. Kore, epilepsi ve kardiyak sorunları olan bir hasta genellikle nöroakantositoz sendromunu düşündürür ve kesin tanı ayrıntılı bir genetik incelemeye bağlıdır. Biz burada, daha sonra koreiform hareketler ve tikler geliştiren, yürüme güçlüğü olan ve bu sebeplerle sosyal problemler yaşayan 57 ve 39 yaşındaki erkek hastaları sunuyoruz. Periferik yayma incelemesinde görülen akantositoz ve genetik incelemede tespit edilen yeni ve nokta mutasyon sonucunda hastalara McLeod sendromu tanısı konulmuştur.

Anahtar Sözcükler: Kore, McLeod Sendromu, nokta mutasyon, nöroakantositoz, XK gen, yeni mutasyon.