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A 6-Year-Old Saudi Boy with Myotonia Congenita

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ABSTRACT

Background: myotonia congenita is an inherited form of myotonia that is due to mutations in the skeletal muscle chloride channel CLCN1. These mutations lead to reduced sarcolemmal chloride conductance, causing delayed muscle relaxation that is evident by clinical exam and myotonic discharges on electromyogram. Two forms of myotonia congenita are recognized: autosomal recessive (Becker variant) or autosomal dominant (Thomsen variant). The recessive form tends to be more severe and has an earlier onset than the dominant one. The dominant form varies in severity from asymptomatic to moderately severe. These two forms may be distinguished by clinical presentation, inheritance pattern and age of onset.

Methods: we described the clinical presentation and genetic testing results of one individual with the autosomal recessive variant of myotonia congenita.

Results: the initial diagnosis was made based on the clinical presentation then it was confirmed based on electromyographic findings of myotonic discharges and CLCN1 gene sequencing which revealed homozygous disease-associated C ->A transverse mutation. The patient achieved a modest response to treatment with phenytoin, carbamazepine or acetazolamide. His condition remained stable with minimal weakness and muscle hypertrophy.

Conclusions: myotonia congenita is a rare genetic disorder of muscle relaxation. The diagnosis is made based on clinical features and is confirmed by sequencing CLCN1 gene. Response to treatment is variable. Recommended medications included mexiletine, phenytoin, carbamazepine and acetazolamide among others.

Kew words: myotonia, congenita, CLCN1.

INTRODUCTION

Myotonia is an impairment of muscle relaxation after voluntary forceful contraction. It could be found in several clinical disorders with different etiologies. One of these disorders, Myotonia Congenita (MC), which is inherited myotonia due to a mutation in the skeletal muscle chloride channel CLCN1.

A defect in CLCN1 (a gene coding for the chloride channel ClC-1) leads to reduced sarcolemmal chloride conductance, which in turn allows the muscle to be hyperpolarized, causing delayed relaxation evident as clinical and electrical myotonia [1].

MC is inherited in autosomal dominant or recessive forms. The recessive form, known as Becker MC, tends to be more severe and has an earlier onset than the dominant one. The dominant form varies in severity from asymptomatic to moderately severe and is known as Thomsen MC.

These two forms may be distinguished by clinical presentation, inheritance pattern and age of onset. Patients with the Becker variant usually present during early childhood, showed pronounced muscle hypertrophy and typically have transient (and occasionally permanent) weakness. Patients affected by the Thomsen variant did not characteristically show significant muscle hypertrophy and the age of onset varied from infancy to adulthood [2].

METHODOLOGY

Method

We reported the clinical presentations of a child with Myotonia Congenita (MC). The study was done after approval of ethical board of King Faisal Specialist Hospital and Research Center-Jeddah.

Genetic Testing

After having obtained written informed consent from patient's parents, blood samples were collected and genomic DNA was extracted according to standard methods. Molecular analysis of the CLCN1 gene was performed by PCR amplification of highly purified genomic DNA, followed by automated uni-directional DNA sequencing of the coding region (23 exons, 3093 bp) of the CLCN1 gene.

Also, ten bases of intronic DNA surrounding each exon including the highly conserved flanking intronic sequence of the exon-intron splice junction for all 23 exons were also sequenced. All abnormal sequence variants were confirmed by bi-directional sequencing. Studies conducted by Athena Diagnostics, Inc. indicate that mutation in this gene and similar sequencing test are detectable at an overall sensitivity approaching 99%. All test result was reviewed, interpreted, and reported by ABMG certified Clinical Molecular Geneticists.

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CASE REPORT

This was a six-year-old boy, a product of full-term pregnancy with uncomplicated antenatal and natal history. Postnatally, the patient had mild respiratory distress and resolved within two days and the baby was discharged home in stable condition. Motor development was fine. The patient was

able to sit at the age of six months and walked at the age of one year. At the age of 18 months, family noticed that the patient has difficulty in initiation of movement especially during running (first few seconds of running), difficulty in getting up from sitting position on the floor and they noticed these symptoms tend to improve with ongoing exercise (warm-up phenomena), and they worsen when the child is exposed to cold climate. There was no swallowing abnormality, no dysphagia, no shortness of breath, no chest pain, no relation to the specific meal and no history of electrolyte imbalance.

The family history is positive for similar symptoms in his 3-year old sister and two first cousins. On physical examination, he was noted to have remarkable myotonia in both hands in response to percussion by tendon hammer and also difficulty in sudden relaxation of the fists of the hands. Mild increase in muscular bulk was observed. No weakness or abnormal movements were noted. Electrolytes and CK levels were normal. EMG was obtained on the right deltoid, right pronator teres, right first dorsal interosseous as well as right tibialis anterior. It revealed increased insertional activities, and myotonic discharges in all muscle tested except first dorsal interosseous. Motor unit action potentials were relatively within normal limits. Recruitment pattern was within normal limits. We sampled the needle examination in the mother, father and younger sister. The younger sister was also positive for myotonic discharges.

CLCN1 DNA sequencing test was done and confirmed the presence of homozygous disease-associated C ->A transversion in the CLCN1 gene.

The preferred medication therapy for this condition, mexiletine, is unfortunately not available in our center. So, the patient was treated initially with phenytoin (50 mg BID), then acetazolamide (125 mg bid) and carbamazepine (300 mg bid) with modest improvement. His condition remained stable with minimal weakness and muscle hypertrophy.

DISCUSSION

The CLCN1 gene belongs to the CLC family of genes, which provide instructions for making chloride channels called ClC-1. These channels, which transport negatively charged chlorine ions, play a key role in a cell's ability to generate and transmit electrical signals. These channels are abundant in skeletal muscles. Muscle contraction and relaxation are controlled by the flow of certain ions into and out of muscle cells. ClC-1 channels are made of two identical protein subunits, each produced from the CLCN1 gene. More than 80 mutations in the CLCN1 gene have been identified in people with myotonia congenita. Most of these mutations cause the autosomal recessive form of the disorder (Becker disease). Becker disease results when CLCN1 mutations change the structure or function of both protein subunits that make up the ClC-1 channel. The altered channels greatly reduce the flow of chloride ions into skeletal muscle cells, which triggers prolonged muscle contractions. Abnormally sustained muscle contractions are the hallmark of myotonia[(3).]

CLCN1 mutations also cause the autosomal dominant form of myotonia congenita (Thomsen disease). A study suggested that the CLCN1 mutations are responsible for Thomsen disease change one of the two protein subunits that make up the ClC-1 channel. The altered protein takes on new, but harmful, properties that disrupt the ability of both subunits to regulate chloride ion flow. Reduced movement of chloride ions into skeletal muscle cells leads to myotonia, which underlies the stiffness and other muscle problems in patients with myotonia congenita [4].

A complementary DNA for a human skeletal muscle chloride channel (CLC-1) was cloned, physically localized on chromosome 7 and linked to the T-cell receptor [beta] (TCRB) locus. An unusual restriction site in the CLC-1 locus in two Becker disease families identified a mutation associated with that disease, a phenylalanine-to-cysteine substitution in putative transmembrane domain D8. This suggests that different mutations in CLC-1 may cause dominant or recessive myotonia [3].

For those patients with mild symptoms, no specific drug treatment may be needed, although it is important to provide advice regarding the avoidance of precipitating factors such as cold exposure or strenuous exercise. In patients with significant symptoms and disability from myotonia, a variety of agents have been suggested. No drugs are available which specifically act on the CLCN-1 channel. Some experimental approaches may have future implications for the treatment of myotonia congenita [5,6]. The class Ib anti-arrhythmic mexiletine is considered to be the first-line treatment of choice [7]. A randomized

controlled trial study of patients with non-dystrophic myotonia compared the use of mexiletine with placebo and showed that the drug resulted in improved patient-reported stiffness over four weeks of treatment [8].

A study of acetazolamide use in the non-dystrophic myotonias have not been performed and there was evidence of some benefits, it was not considered as a first line agent for the treatment of myotonia [5]. Anti-convulsants, local anesthetics and anti-arrhythmic drugs which block sodium channels are the most frequently used agents in the treatment of myotonia. Phenytoin has been shown to improve the righting time of myotonic mice turned onto their backs [9].

CONCLUSION

Myotonia congenita is a rare genetic disorder of muscle relaxation. The diagnosis is made based on clinical features and is confirmed by sequencing CLCN1 gene. Response to treatment is variable. Recommended medications include mexiletine, phenytoin, carbamazepine and acetazolamide among others.

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