Moroccan consanguineous family with Becker myotonia and review

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Abstract

Myotonia congenita is a genetic muscle disorder characterized by clinical and electrical myotonia, muscle hypertrophy, and stiffness. It is inherited as either autosomal-dominant or –recessive, known as Thomsen and Becker diseases, respectively. These diseases are distinguished by the severity of their symptoms and their patterns of inheritance. Becker disease usually appears later in childhood than Thomsen disease and causes more severe muscle stiffness and pain. Mutations in the muscular voltage-dependent chloride channel gene (CLCN1), located at 7q35, have been found in both types. We report here the case of a Moroccan consanguineous family with a myotonic autosomal-recessive condition in two children. The molecular studies showed that the patients reported here are homozygous for mutation p.Gly482Arg in the CLCN1 gene. The parents were heterozygote carriers for mutation p.Gly482Arg. This diagnosis allowed us to provide an appropriate management to the patients and to make a genetic counselling to their family.

Key Words

Autosomal recessive, CLCN1 gene, myotonia congenital

Introduction

Myotonia congenita (MC) is a genetic muscle disorder characterized by clinical and electrical myotonia, muscle hypertrophy, and stiffness.[1] Its prevalence is quite variable among different populations, with a reported range of 0.2–0.9 per 100,000 inhabitants in Caucasian populations,[2,3] and with clustering in some regions like northern Finland, where a Figure of 7.3 per 100,000 inhabitants has been found.[3] It is inherited as either autosomal-dominant or –recessive, known as Thomsen and Becker diseases, respectively.[3] The specific prevalence of Becker’s myotonia is estimated to be 1:25,000.[4] Compared with Thomsen’s MC, Becker’s disease is more common, more insidious and has initial symptoms that occur later in childhood.[5] Mutations in the muscular voltage-dependent chloride channel gene (CLCN1), located at 7q35, have been found in both types.[1]

We report here the case of a Moroccan consanguineous family with a myotonic autosomal-recessive condition in two children. The molecular studies showed that the patients reported here are homozygous for mutation p.Gly482Arg in the CLCN1 gene.

Case Report

A 10-year-old boy (case 1) was referred with complaints of lower limb pain and weakness for 7 years duration. He is a Moroccan consanguineous child (first degree), the third of four children, with no relevant familial history. It was difficult for him to initiate strong muscle contractions, but this improved with continued exercise. The symptoms were slightly worse during winter and stress. He had bilateral calf and thigh cramping, with tightness occurring when he ran, ascended stairs, or participated in sports. These episodes sometimes caused him to fall. His younger sister (case 2) was 4-years-old and had intermittent muscle cramping of rapid movements. Both of them exhibited proximal and distal muscle weakness. The myotatic reflexes were lessened and the sensibility was normal. Muscular hypertrophy, predominantly in the lower limbs, and joint retraction, predominantly in hands, feet, and ankles, were found only in the older child. His examination also revealed a stiff gait and an inability to walk on the heels bilaterally. He also had exacerbation of symptoms with cold temperatures. Not one of the two
children had dysphagia. Investigations revealed an elevated serum creatine kinase concentration level of 430 U/L and 331 U/L (normal, 0–170 U/L) for, respectively, the boy and the girl [Table 1]. Nerve conduction studies for the two children revealed normal amplitudes of motor potentials in the upper and lower limbs. Electromyography of the tibialis anterior and the medial gastrocnemius demonstrated profuse myotonic discharges in the two suffers, but it was more profuse in the boy. Motor unit potentials in both muscles were of normal morphology. Repetitive nerve stimulation of the right median nerve to abductor pollicis brevis (APB) showed compound muscle action potential (CMAP) decrements. The parents and the two other children were free of any such symptoms. Their clinical neurological examination was completely normal.

Before these characteristic clinical and electrophysiological features, the diagnosis of Becker myotonia was considered. Informed consent was obtained from the probands’ parents prior to implementation of the genetic studies reported here. Peripheral blood was collected from the proband, his sister, and their parents. Molecular genetic testing for suspected Becker myotonia was performed by DNA-sequence analysis of all CLCN1 gene exons and flanking intronic sequences. As a result, we identified the mutation p.Gly482Arg in homozygosis in both patients [Figure 1]. As expected, the parents were heterozygote carriers for mutation p.Gly482Arg.

Discussion

MC is an inherited neuromuscular disorder characterized clinically by involuntary muscle contractions and electrophysiologically by myotonic discharges.[8] MC exists in two variants: MC Thomsen, with autosomal-dominant inheritance, and MC Becker with a recessive inheritance.[1] These diseases are distinguished by the severity of their symptoms and their patterns of inheritance.[2] Becker disease usually appears later in childhood than Thomsen disease and causes more severe muscle stiffness and pain. Typically, the stiffness is maximal at the commencement of activity, and improves with repeated contractions (“warm-up” phenomenon).[1] Patients suffering from Becker disease often experience temporary attacks of muscle weakness, particularly in the arms and hands, brought on by movement after periods of rest. They may also develop mild, permanent muscle weakness over time.[2,3]

Other than clinical history, mode of inheritance, and neurological examination, electrophysiological studies are an important part of the initial evaluation of patients with muscle stiffness.[3] Both forms are caused by mutations in the muscular voltage-dependent chloride channel gene (CLCN1) in 7q35. Several mutations are associated with both recessive and dominant MC.[4] More than 100 mutations in the CLCN1 gene have been identified that are associated with MC.[4] The mutation frequencies in MC indicate that none of them is highly prevalent. Although some CLCN1 mutations have been reported to be more frequent in Caucasian populations like R894X, F413C, M485V, and A531V.[14-20] [Table 2], an accurate value for the frequency of these mutations has not been published for any population. Mutation Gly482Arg was identified in 1995 by Meyer-Kleine et al.[15] as a recessive mutation in two nonconsanguineous families. Jou et al.[11] have reported one Taiwanese family with the same mutation in a recessive pedigree and Lin et al.[12] have proved by functional analysis of the Clc-1 mutant its deleterious

Table 1: Clinical features of Becker myotonia

| Clinical features                  | Case 1 | Case 2 |
|-----------------------------------|--------|--------|
| Onset 4 to 12 years old           | +      | +      |
| Muscle pain                       | +      | -      |
| Muscle cramps                     | +      | +      |
| Transient weakness                | +      | +      |
| Generalized stiffness             | +      | -      |
| Predominance on legs              | +      | +      |
| Tongue myotonia                   | -      | -      |
| Dysphagia                         | -      | -      |
| Percussion myotonia               | +      | +      |
| Handgrip myotonia                 | +      | +      |
| Generalized hypertrophy           | +      | -      |
| Warm up                           | +      | +      |
| Exacerbation with cold temperatures| +      | -      |
| Serum creatine kinase concentration| +      | +      |

≥3–4-times the upper limits of normal
effect. Conservation through evolution of amino acid Gly482 anticipated its essential role in Clc-1 function. Segregation in the family presented here corresponds to a recessive pattern of inheritance as the parent’s patients were asymptomatic. We examined first the older brother who was more severely affected than his young sister. He originally presented for investigation of recurrent episodes of weakness and pain that developed during sustained muscle contraction.

In conclusion, we report here a Moroccan consanguineous family with autosomal-recessive congenital myotonia due to a homozygous mutation of the CLCN1 gene. To the best of our knowledge, there is no data about the prevalence of this disease in the Moroccan population but, given the high rate of consanguinity in Moroccans (15.25%),[35] the incidence of myotonic Becker should probably be higher than we think in the Moroccan population.

Adequate clinical diagnosis of MC would allow focusing the molecular studies toward the confirmation of the initial diagnosis, leading to a proper clinical management, genetic counselling and improvement in the quality of life of the patients and relatives. Management of MC includes learning to accommodate the activities and lifestyle to reduce symptoms and pharmacologic treatment of myotonic stiffness, mainly Mexiletine, a lidocaine derivative.

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