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Original Article

Spectrum of Nondystrophic Skeletal Muscle Channelopathies in Children

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ABSTRACT

BACKGROUND: The nondystrophic skeletal muscle channelopathies are a group of disorders caused by mutations of various voltage-gated ion channel genes, including nondystrophic myotonia and periodic paralysis. **METHODS:** We identified patients with a diagnosis of muscle channelopathy from our neuromuscular database in a tertiary care pediatric center from 2005 to 2015. We then performed a retrospective review of their medical records for demographic characteristics, clinical features, investigations, treatment, and follow-up. **RESULTS:** Thirty-three patients were identified. Seventeen had nondystrophic myotonia. Seven of them had chloride channelopathy (four Becker disease and three Thomsen disease). Warm-up phenomenon and muscle hypertrophy were common clinical manifestations in this subgroup. Ten patients had sodium channelopathy (four paramyotonia congenita and six other sodium channel myotonia). Stiffness of the facial muscles was an important presenting symptom, and eyelid myotonia was a common clinical finding in this subgroup. The majority of these patients had electrical myotonia. Mexiletine was effective in controlling the symptoms in patients who had received treatment. Sixteen children had periodic paralysis (four hyperkalemic periodic paralysis, eight hypokalemic periodic paralysis, and four Andersen-Tawil syndrome). Acetazolamide was commonly used to prevent paralytic attacks and was found to be effective. **CONCLUSIONS:** Nondystrophic muscle channelopathies present with diverse clinical manifestations (myotonia, muscle hypertrophy, proximal weakness, swallowing difficulties, and periodic paralysis). Cardiac arrhythmias are potentially life threatening in Andersen-Tawil syndrome. Timely identification of these disorders is helpful for effective symptomatic management and genetic counseling.

Keywords: nondystrophic myotonia, periodic paralysis, skeletal muscle channelopathies, children, muscle disorders

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Introduction

The skeletal muscle channelopathies represent a rare group of neuromuscular disorders that are caused by genetic mutations in different voltage-gated ion channels.[1,2] These channels involve various cation (sodium, potassium, and calcium) or anion (chloride) channels that play an important role in depolarizing the muscle membrane. Muscle channelopathies are broadly divided into two main categories: nondystrophic myotonias (NDMs) and periodic paralysis (PP).[1-4] The hallmark clinical manifestation for NDM is myotonia (i.e., delayed relaxation after muscle contraction),[5] whereas in PP it is episodic muscle weakness.[1] Clinical manifestations of channelopathies depend on the net effect of depolarization on the muscle membrane, which can be more excitable causing NDM or less excitable causing PP.[1] In the case of NDM, muscle stiffness can cause significant functional impairment,[6] and in the case of PP, episodic weakness can be disabling. As these disorders are rare and have diverse clinical manifestations, there is frequently a delay in making the diagnosis.

We describe our experience with skeletal muscle channelopathies in children who were evaluated and treated in a tertiary care pediatric neuromuscular clinic.

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TABLE 1.
Clinical Characteristics, Investigations, Treatment of Patients With Nondystrophic Myotonia

Diagnosis	Age of Presentation/ Sex	Family History	Presenting Symptoms	Warm-up Pheno-menon	Cold Sensitivity/ Paradoxical Myotonia	Muscle Hyper-trophy	Percussion or Grip Myotonia/ Eyelid Myotonia	EMG	Genetic Mutation	Treatment/ Response
1. Becker MC	7 y/M	−	Limb stiffness	+	−/−	+	−/−	Myotonia	CLNC1: c.1012C>T and c.774G>A	Mexiletine (200 mg b.i.d.)/ significant improvement
2. Becker MC	6 y/M	−	Limb stiffness (lower limb predominant), transient leg weakness	−	−/−	+	+/−	Myotonia	CLCN1: c.2680C>T, p.Arg894X and c.180+3A>T	Mexiletine (100 mg b.i.d.)/ significant improvement
3. Becker MC	8 y/F	−	Limb stiffness (lower limb predominant)	+	−/−	−	+/−	Myotonia	CLCN1: c.1129C>T, p.Arg377X and c.2680C>T, p.Arg894X	None
4. Becker MC	3 y/F	−	Limb stiffness	+	−/−	−	+/−	Myotonia	CLCN1: c.1679T>C, p.Met560Thr and c.1238T>G, Phe413Cys	Mexiletine (150 mg b.i.d.)/ significant improvement
1. Thomsen MC	2 y/M	−	Limb stiffness	+	−/−	+	+/+	Myotonia	Pathogenic mutation of CLCN1	Mexiletine (300 mg b.i.d.)/ significant improvement
2. Thomsen MC	6 y/M	+	Limb stiffness	+	−/−	+	+/+	Myotonia	CLCN1: c.830C>A, p. Thr268Lys	Mexiletine (150 mg b.i.d.)/ significant improvement
3. Thomsen MC	3 m/F	+	Swallowing difficulty	+	−/−	−	+/−	Myotonia	CLCN1: c.1606G>A, p. Val536Ile	None
1. PMC	2 y/F	+	Face and limb stiffness	−	+/−	−	+/+	Myotonia	SCN4A: c.1333G>A, p.Val445Met	Mexiletine (150 mg b.i.d.)/ moderate improvement
2. PMC	6 m/F	+	Face and limb stiffness, transient weakness	−	+/+	−	+/−	Myotonia	SCN4A: c.3938C>T, p.Thr1313Met	Stopped due to side effects
3. PMC	6 y/M	+	Face and limb stiffness	−	+/−	+	−/−	Myotonia	SCN4A: c.3877G>A, p.Val1293Ile	Mexiletine (300 mg b.i.d.)/ significant improvement
4. PMC	2 y/M	+	Limb stiffness	−	+/+	−	−/+	Myotonia	SCN4A: p.Gly1306Ala	None
1. Other SCM	6 y/M	+	Face and limb stiffness	−	−/−	−	+/+	Myotonia	SCN4A: c.3478A>G, p.Ile 1160Val	Acetazolamide (250 mg b.i.d.)/ Significant improvement
2. Other SCM	5 y/M	+	Face stiffness	−	−/−	+	+/+	Not done	SCN4A: c.1333G>A, p.Val445Met	None
3. Other SCM	3 y/M	+	Face and limb stiffness	+	−/−	+	+/+	Not done	SCN4A: c.3917G>C, p.Gly1306Ala	None

(*continued on next page*)