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Case Series

Myotonia congenita: A case series

Bhuvaneshwari Rajendran[1]

[1]Consultant Neurophysiology and Neurology, Kauvery Hospital Alwarpet, Chennai
*Correspondence: bhuvana1675@hotmail.com

Abstract: This study examines five patients with confirmed CLCN1 gene mutations associated with myotonia congenita, a rare neuromuscular disorder causing muscle stiffness. Four patients presented milder symptoms with early onset, while one exhibited severe phenotype affecting facial muscles. All patients maintained ambulatory function, though the severe case required a walking stick. Notably, none reported family history, suggesting de novo mutations or incomplete penetrance. The study highlights the phenotypic variability in CLCN1-related myotonia, emphasizing the importance of genetic testing for accurate diagnosis and counseling. The findings contribute to understanding genotype-phenotype relationships in myotonia congenita and stress the need for comprehensive clinical assessments in suspected cases.

Keywords: Muscle disorders; genetic myopathy; muscle stiffness; clinical features; inheritance patterns

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1. Introduction

Myotonia congenita is a rare genetic neuromuscular disorder characterized by the delayed relaxation of muscles after voluntary contraction, a phenomenon known as myotonia. This condition affects the skeletal muscles, causing muscle stiffness, cramping, and, in some cases, hypertrophy (increased muscle size). Myotonia congenita can manifest in two primary forms: Thomsen disease and Becker disease, which differ in their inheritance patterns and symptom severity.

1.1. Pathophysiology

Myotonia congenita is caused by mutations in the CLCN1 gene, which encodes the chloride channel (ClC-1) in skeletal muscle cells. These channels are responsible for stabilizing muscle membrane excitability by regulating chloride ion flow. Mutations in the CLCN1 gene reduce the ability of chloride ions to flow through the channel, resulting in prolonged muscle contractions after stimuli, as the muscle fibres are unable to return to their resting state quickly. The severity of myotonia varies depending on the specific mutation and its impact on chloride channel function.

1.2. Forms of Myotonia Congenita

1.2.1. Thomsen Disease (Autosomal Dominant)

1. Thomsen disease is the less severe form and is inherited in an autosomal dominant manner. This means that only one copy of the mutated gene is needed for the disorder to manifest.
2. Symptoms often appear in early childhood but tend to be milder compared to Becker disease.
3. Muscle stiffness usually affects the legs, but other muscle groups can be involved. The stiffness is typically transient, and once movement is initiated, the stiffness lessens (a phenomenon known as the warm-up effect).

1.2.2. Becker Disease (Autosomal Recessive)

1. Becker disease is the more severe form and is inherited in an autosomal recessive pattern, meaning both copies of the CLCN1 gene must be mutated for the condition to develop.
2. Symptoms generally appear later, often in adolescence, and are more pronounced. Muscle stiffness is more severe, especially after periods of rest.
3. Muscle hypertrophy, particularly in the legs and arms, is more prominent in Becker disease. In contrast to muscle hypertrophy, there may be weakness in some cases.
4. Becker disease tends to affect more muscle groups, and the myotonia can interfere with daily activities like walking, running, and gripping objects.

1.2.3. Symptoms

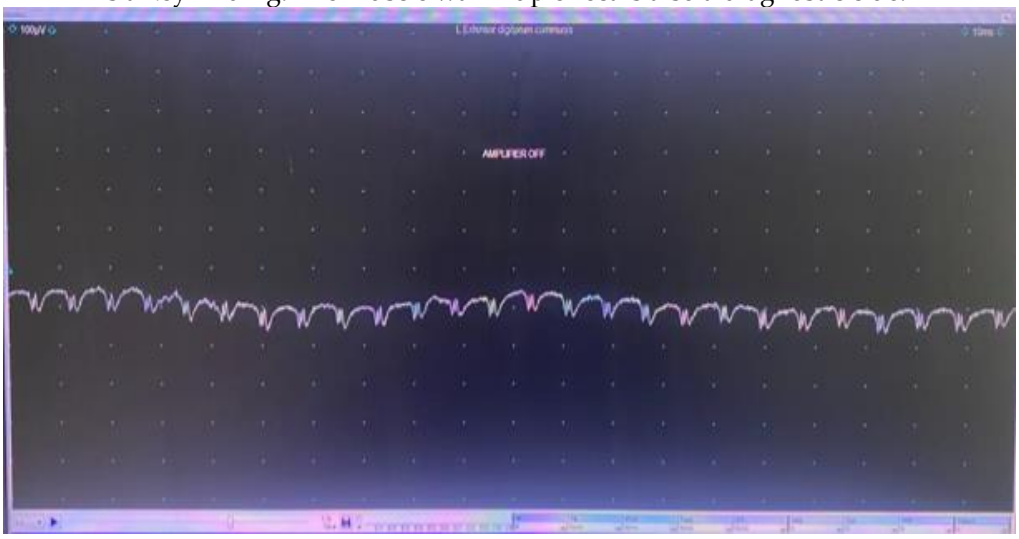
The hallmark symptom of myotonia congenita is muscle stiffness, which can affect various parts of the body. The severity of symptoms varies, but common manifestations include:

1. Muscle stiffness and delayed relaxation: This is particularly noticeable after rest or inactivity. The stiffness tends to improve with repeated movement (warm-up phenomenon).
2. Difficulty with movement: Stiffness may make it challenging to initiate movement, such as rising from a chair, running, or gripping objects.
3. Muscle hypertrophy: Individuals with myotonia congenita often have larger-than-average muscles due to continuous muscle activity.
4. Transient weakness: In Becker disease, patients may experience temporary muscle weakness, particularly after sustained activity.
5. Improvement with exercise: Some individuals report that symptoms lessen with regular physical activity, though this may vary from person to person.

1.2.4. Diagnosis

Diagnosis of myotonia congenita is based on clinical evaluation, family history, and diagnostic tests. Common diagnostic methods include:

1. Electromyography (EMG): EMG testing can detect the electrical activity in muscles, revealing the characteristic prolonged discharges seen in myotonia.
2. Genetic Testing: A definitive diagnosis can be made through genetic testing to identify mutations in the CLCN1 gene.
3. Physical Exam: Muscle stiffness, particularly after brief periods of inactivity, is a key finding. The muscle warm-up effect is also a diagnostic clue.



EMG

1.2.5. Treatment

There is no cure for myotonia congenita, but treatment aims to manage symptoms and improve quality of life. Treatment options include,

Medications:

1. Mexiletine: A sodium channel blocker, it is often the most effective medication for reducing muscle stiffness and myotonia.
2. Carbamazepine or Phenytoin: These anticonvulsants can also help with myotonia, though they are used less frequently.
3. Acetazolamide: This carbonic anhydrase inhibitor may be used in some cases to reduce myotonia.

Physical Therapy: Exercise and stretching can help manage stiffness and prevent muscle atrophy.

Lifestyle Modifications: Regular physical activity can reduce symptom severity by utilizing the warm-up phenomenon, improving overall muscle function.

Prognosis: The prognosis for individuals with myotonia congenita is generally good. While the condition can cause significant muscle stiffness and discomfort, life expectancy is normal, and with proper management, individuals can lead active lives. Many patients experience improvement in symptoms with age or regular physical activity. The severity of symptoms can vary widely, with those affected by Becker disease typically experiencing more significant challenges than those with Thomsen disease.

2. Case Presentation

We have 5 genetically proven patients with mutations in the CLCN1 gene. Four of them have relatively lesser impact and less clinical muscle stiffness and with early onset of symptoms.

One of them has severe muscle stiffness including facial muscles and peri-orbital muscles.

All of them are ambulant and very functional except the severely affected patient needs a walking stick while walking for support. None of them have a positive family history.

S. No	Gender	Age of onset	Severity	Treatment	Possible Variant
1	Female	3	Very Mild	Nil	Possible Thomsen
2	Male	5	Mild to moderate	Carbamazepine	Possible Thomsen
3	Male	4	Mild	Nil so far.	Possible Thomsen
4	Female	5	Mild to moderate	Mexiletine	Possible Thomsen
5	Male	10	Severe	Mexilitene. Phenytoin did not help in the past	Becker type

3. Conclusions

Myotonia congenita is a rare but manageable genetic disorder caused by mutations in the CLCN1 gene. It results in muscle stiffness and delayed relaxation after voluntary contractions, with varying degrees of severity depending on the form (Thomsen or Becker disease). Early diagnosis and appropriate management, including medications and physical therapy, can help mitigate symptoms and improve quality of life for affected individuals.

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