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Case Report

Lid Lag Phenomenon Revealing Myotonia Congenita: Case Report

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Abstract

Myotonic disorders represent rare, genetically heterogeneous neuromuscular diseases, whose clinical hallmark is the presence of myotonia. Myotonic disorders are generally classified as either dystrophic (DM) or non-dystrophic myotonia (NDM). Non-dystrophic myotonias (NDM) are skeletal muscle channelopathies characterized by a disruption of normal sarcolemmal ion conductance that results in abnormal muscle fiber excitability. Depending on the affected ion channels, non-dystrophic myotonias include myotonia congenita (MC), paramyotonia congenita (PMC) and sodium channel myotonia (SCM).

Myotonia congenita (MC) is the most common type of non-dystrophic myotonia, occurring due to mutations in CLCN1, the gene encoding the primary skeletal muscle voltage-gated chloride channel (ClC-1). Diagnosis is suspected in the setting of myotonia, muscular stiffness, the warm-up phenomenon, family history and electromyographic studies suggestive of myotonia congenita and is ultimately established through genetic testing.

In this case report, we present a 9-year-old male patient with complaints of muscular stiffness, difficulty in climbing stairs, with calf and buttock hypertrophy and percussion myotonia in both hands and calves evident in physical examination. A diagnosis Myotonia Congenita was made based on the presence of a positive Lid lag sign, a positive warm up test and the results of electromyography (EMG) studies. It was then confirmed by genetic testing.

Along with showcasing a rare pathology, this case report emphasises the importance of a thorough clinical evaluation and electrophysiological studies as the best initial assessments of myotonia, when considering the differential diagnosis and in guiding appropriate genetic testing.

Keywords: *Non-Dystrophic Myotonia; Channelopathies; Myotonia Congenita; Electrophysiology*

Introduction

Myotonia congenita (MC) is the most common skeletal muscle channelopathy with an estimated prevalence between 1:23,000 and 1:50,000 for the recessive variant and a lower prevalence for the dominant variant [1-3]. Mutations in the *CLCN1* gene, located in chromosome 7q35, that codes for the main skeletal muscle voltage-gated chloride channel (ClC-1) are the culprit for the disorder [3]. These

loss-of-function mutations are responsible for the deficient chloride influx, which causes sarcolemmal hyperexcitability that is clinically manifested as myotonia [4,5]. Myotonia is defined clinically as incomplete or delayed relaxation of muscle after voluntary contraction or percussion [6]. Myotonia congenita can have an autosomal dominant inheritance pattern (Thomsen disease, OMIM 160800) or an autosomal recessive pattern (Becker disease, OMIM 255700) [7,8]. Both types present with similar clinical features but can be discerned from one another based on their mode of inheritance, age of onset, characteristics and severity of their clinical presentation [7]. Extensive phenotypic variability of the condition exists even within members of the same family [9].

Thomsen disease is the autosomal dominant variant of myotonia congenita and may be evident in early infancy with delayed relaxation of the eyelids after closure during crying or sneezing [7,10,11]. However, commonly the diagnosis is established during late childhood with complaints of muscular stiffness, clumsiness and difficulties with movements after rest [12-14]. Mild hypertrophy predominantly in the lower limbs may be present [7,13]. Clinical presentation may vary from asymptomatic or mild, with patients unaware of their condition (latent myotonia), to moderate and rarely severe [7]. Generally, Thomsen Disease causes mild to moderate myotonia associated with a normal life expectancy [15].

Becker disease is the autosomal recessive variant of myotonia congenita and is frequently diagnosed in early childhood [16,17]. Unlike Thomsen Disease that affects specific muscle groups, Becker Disease causes generalized myotonia that involves all muscles. Moderate or marked muscular hypertrophy is present [17]. Clinical distinctions with Thomsen Disease other than age of onset and severity of myotonia, include the presence of transient weakness upon movement initiation, particularly after prolonged rest and occasionally painful muscle cramps and myalgia during rest [17-19].

Considerable clinical overlap exists between both types with common clinical findings such as an inability to relax after prolonged contraction, spontaneous muscle contraction after direct percussion (percussion myotonia), lid lag sign may be seen on suddenly looking downwards after prolonged upwards gaze and the warm-up phenomenon, improvement of myotonia and stiffness from voluntary repetitive movements [7,11-13,15].

Diagnosis of myotonia congenita is suspected in the presence of the aforementioned clinical findings and electromyography studies showing continued, repetitive high-frequency discharges (myotonic bursts) that guide appropriate genetic testing.

Genetic testing represents the gold standard of establishing the diagnosis, with the most common one being sequence analysis of *CLCN1* followed by gene targeted deletion/duplication analysis if sequence analysis is inconclusive [20]. More in-depth molecular testing includes multigene panel testing, exome sequencing, genome sequencing, mitochondrial sequencing [20].

Other types of non-dystrophic myotonia should be considered in differential diagnosis of myotonia congenital MC, specifically paramyotonia congenita PMC and sodium channel myotonia SCM. It is crucial to exclude dystrophic myotonia DM type 1 and DM type 2 when considering a diagnosis of myotonia congenital.

Treatment of myotonia congenita consists in both a pharmacological and non-pharmacological approach.

Avoiding triggers that stimulate myotonic episodes is imperative in the management of this condition. When this alone doesn't suffice, medication can be used to help alleviate symptoms. Pharmacological treatment includes the use of mexiletine [21] the medication of choice for this disorder, carbamazepine and phenytoin [22-24]. Uses of quinidine, tocainide, dantrolene and acetazolamide have also been reported [20]. Other non-pharmacological therapies often employed by patients include relaxation techniques and exercises to improve flexibility.

Case Report

In this case report, we present a 9-year-old male patient with complaints of muscle stiffness and difficulty in climbing stairs. On physical examination, the presence of the lid-lag sign and a positive warm-up test were seen (Figure 1). Calf and buttock hypertrophy were also evident (Figure 1).

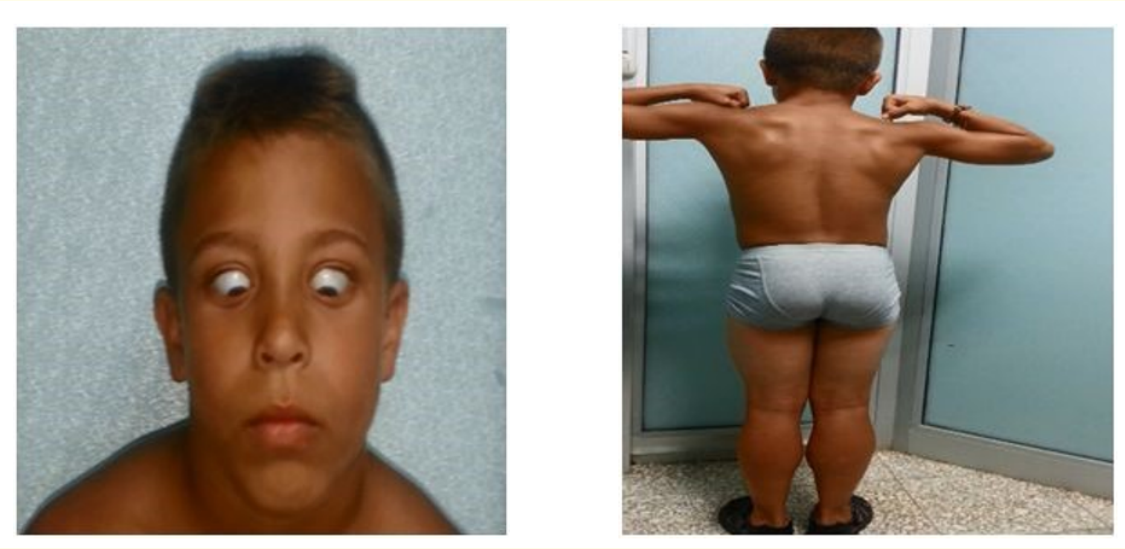


Figure 1

There was percussion myotonia in both calves and hands (Figure 2).

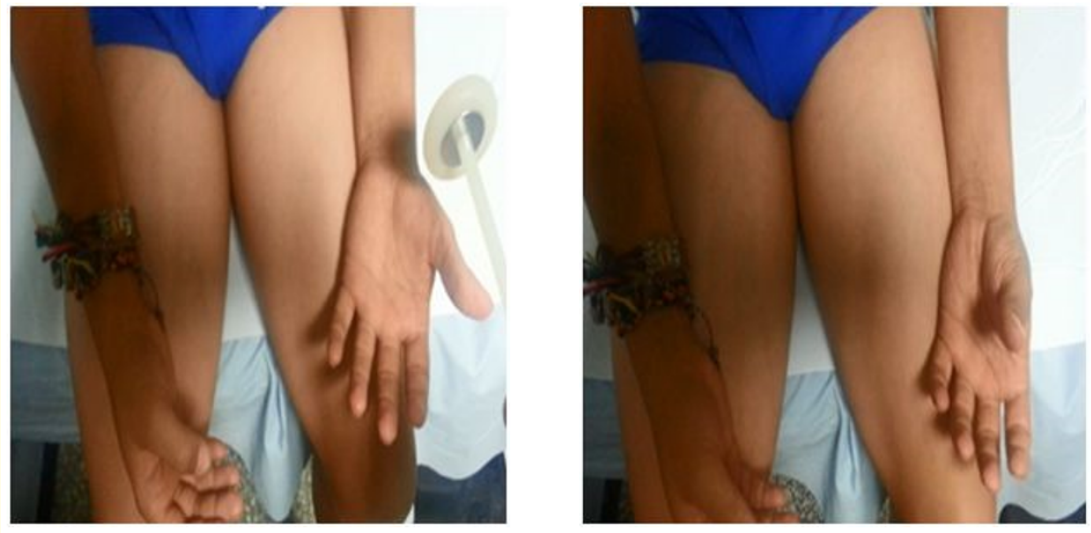
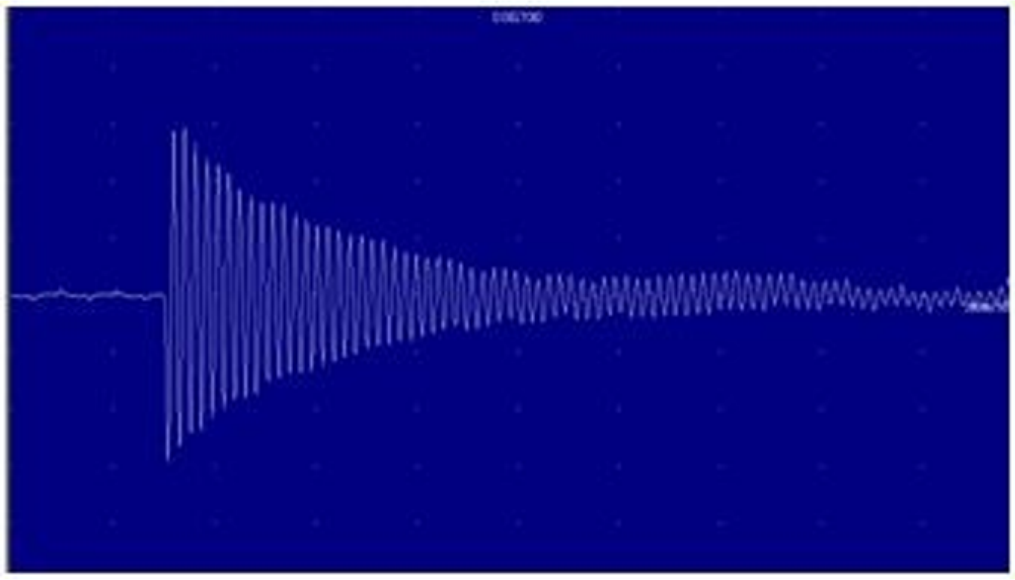
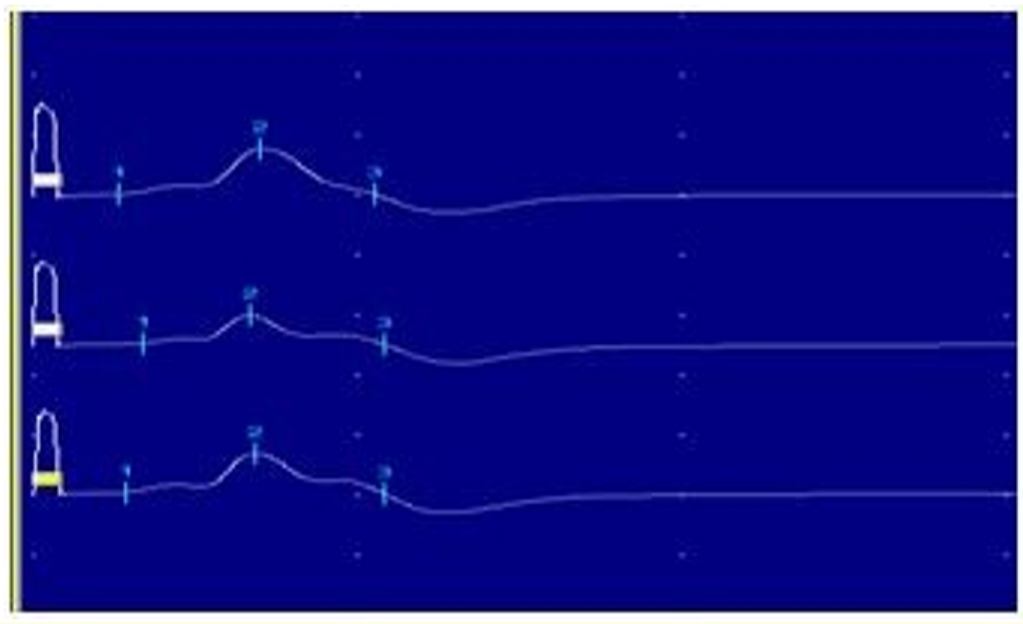


Figure 2

An EDX and EMG test at 31.0 to 35.0C. degree was performed and showed: all nerve conduction velocities, all distal onset latencies, and all CMAP amplitudes were normal and the sensory nerve conduction velocities were normal. Repetitive nerve Stimulation Test: were normal at 3 Hz frequency, but pathological decrement (34%) was evident at High Frequency stimulation. Effort Test had pathological decrement (40%) after ten seconds of effort. Needle EMG Exam demonstrated an increased insertional activity and presence of spontaneous activity of high frequency discharges (Electrical Myotonia). The recruitment pattern was early, brief, with low amplitude and polyphasic changes.





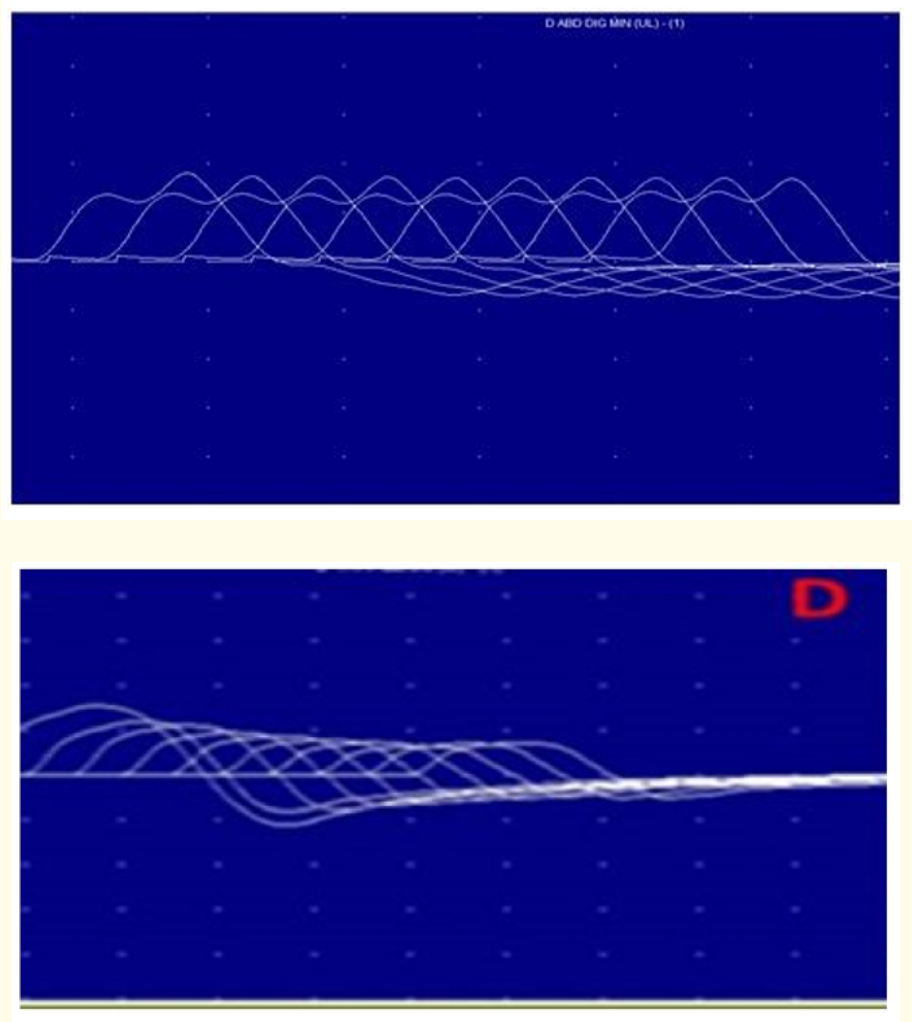


Figure 3

Clinical presentation and electromyography studies (EMG) suggested myotonia congenita. Molecular testing confirmed the diagnosis of autosomal dominant myotonia congenita (Thomsen disease).

Discussion

Myotonia Congenita (MC) was first described by Bryant, Lipicky and colleagues in the early 1960s, as deficient muscle chloride conductance [25]. The first CLCN1 gene mutations for both autosomal dominant and recessive MC were demonstrated in the early 1990s [26,27]. It is well established that impairment of the normal function of a voltage-gated chloride channel in skeletal muscles (ClC-1) due to mutations in *the CLCN1* gene, is central to the pathogenesis of MC. Mutations manifest with wide phenotypic variability. Lossin., *et al*. have described as many as 130 possible mutations in this gene that may express as either dominant or recessive forms of myotonia [7].

This variability may make it hard sometimes to distinguish MC from other non-dystrophic myotonias. It has been attributed to variable expression, incomplete penetrance, the impact of mutant alleles, and intrinsic variability of channel dysfunction [28].

Clinical presentation, physical findings, inheritance pattern, and review of other organ systems are critical to differentiate one form of myotonia from another. Age of onset, effects of temperature, predominant symptoms, and presence of transient weakness help navigate differential diagnosis. Electromyography (EMG) and molecular genetic testing allow easy diagnosis of MC in most circumstances, both of which were used to diagnose the patient in this case report. Although EMG is a beneficial diagnostic tool, it has limited usefulness in differentiating MC from other myotonias [7]. Even molecular genetic testing cannot completely rule out MC in the case of particular mutations.

Several protocols have been suggested in EMG to enhance the sensitivity and specificity in diagnosing myotonic disorders. Long and short exercise tests after cooling and re-warming have been described as one of these protocols. The short exercise tests correlate accurately with DNA based diagnosis [29]. Another proposed method is repetitive nerve stimulation at 3Hz, which has shown high sensitivity and reproducibility in diagnosing autosomal recessive MC cases. Patients with autosomal dominant MC and those suffering from myotonia caused by mutations that don't affect the CLCN1 gene showed negative results [30]. Although not obtained and discussed in detail in this case report, histological features following muscle biopsy may also play a role in diagnosing autosomal recessive MC.

Studies on MC have focused on the clinical presentation, molecular physiology, and genetics of the disorder. These studies suggest that MC is characterized by a variable expression that affects the phenotypic presentation of the disease. Tang., *et al*. observed sporadic mutations in the entire protein sequence, with no association between the pattern of inheritance and the position of mutation, thereby indicating the presence of multiple pathophysiological mechanisms associated with particular mutations [31].

Further attempts to explain these findings involve data from studies in channelopathies as a specific pathologic entity. Research on the severity of muscle channelopathies, Duno., *et al*. found homozygotes express more severe features and compound muscle action potential (AP) changes, compared to heterozygotes. A hundred percent defective ion channels in homozygous individuals account for the most severe phenotype compared to its heterozygous counterpart [32]. However, while casting light on the genotype-phenotype correlation and molecular basis of non-dystrophic myotonic disorders, these findings do not guide treatment choices or aid in early diagnosis.

After receiving a formal diagnosis of myotonia congenita, based on their clinical presentation, electromyography examination, and genetic testing, patients are offered a personalized treatment tailored to their specific characteristics, preferences, and severity.

Conclusion

This case report highlights the importance of a thorough clinical evaluation and electrophysiological studies (EMG studies) in assessing myotonia, distinguishing between numerous congenital and acquired neuromuscular disorders associated with myotonia, and in guiding physicians toward the appropriate genetic testing.

Bibliography

1. Horga A., *et al*. "Prevalence study of genetically defined skeletal muscle channelopathies in England". *Neurology* 80 (2013): 1472-1475.

2. Suetterlin K., *et al*. "Muscle channelopathies: recent advances in genetics, pathophysiology and therapy". *Current Opinion in Neurology* 27 (2014): 583-590.

3. Morales F and Pusch M "An Up-to-Date Overview of the Complexity of Genotype-Phenotype Relationships in Myotonic Channelopathies". *Frontiers in Neurology* 10 (2020): 1404.

4. Koch MC., *et al*. "The skeletal muscle chloride channel in dominant and recessive human myotonia". *Science* 257 (1992): 797-800.

5. Pusch M. "Myotonia caused by mutations in the muscle chloride channel gene CLCN1". *Human Mutation* 19 (2002): 423-434.

6. Michael K Hehir and Eric L Logigian. "Electrodiagnosis of Myotonic Disorders, Physical Medicine and Rehabilitation". *Clinics of North America* 24.1 (2013): 209-220.

7. Lossin C and George AL. "Myotonia Congenita". *Advanced Genetics* 63 (2008): 25-55.

8. Burge JA and Hanna MG. "Novel insights into the pathomechanisms of skeletal muscle channelopathies". *Current Neurology and Neuroscience Reports* 12 (2012): 62-69.

9. Plassart-Schiess E., *et al*. "Novel muscle chloride channel (CLCN1) mutations in myotonia congenita with various modes of inheritance including incomplete dominance and penetrance". *Neurology* 50.4 (1998): 1176-1179.

10. Thomsen J. "Tonische Kra¨mpfe in willku¨rlich beweglichen Muskeln in Folge von ererbter psychischer Disposition (Ataxia muscularis?)". *Arch Psychiatr Nervenkr* 6 (1876): 702-718.

11. Wakeman B., *et al*. "Extraocular muscle hypertrophy in myotonia congenita". *Journal of AAPOS* 12 (2008): 294-296.

12. Trivedi JR., *et al*. "Non-dystrophic myotonia: prospective study of objective and patient reported outcomes". *Brain* 136.7 (2013): 2189-2200.

13. Trip J., *et al*. "Redefining the clinical phenotypes of non-dystrophic myotonic syndromes". *Journal of Neurology, Neurosurgery, and Psychiatry* 80.6 (2009): 647-652.

14. Colding-Jorgensen E. "Phenotypic variability in myotonia congenita". *Muscle Nerve* 32.1 (2005): 19-34.

15. Hahn C and Salajegheh MK. "Myotonic disorders: A review article". *The Iranian Journal of Neurology* 15.1 (2016): 46-53.

16. Becker PE. "Zur Genetik der Myotonien". In "Progressive Muskeldystrophie-Myotonie-Myasthenie" (E. Kuhn, edition.) (1966): 247-255.

17. Becker PE. "Myotonia Congenita and Syndromes Associated with Myotonia". Thieme, Stuttgart (1977).

18. Erich Kuhn S., *et al*. "The autosomal recessive (Becker) form of myotonia congenita". *Muscle and Nerve* 2.2 (1979): 109-117.

19. Rüdel R., *et al*. "Transient weakness and altered membrane characteristic in recessive generalized myotonia (Becker)". *Muscle Nerve* 11(1988): 202-211.

20. Dunø M and Colding-Jørgensen E. "Myotonia Congenita". In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews®. Seattle (WA): University of Washington, Seattle (2005).

21. Statland JM., *et al*. "Mexiletine for Symptoms and Signs of Myotonia in Nondystrophic Myotonia: A Randomized Controlled Trial". *The Journal of the American Medical Association* 308.13 (2012): 1357-1365.

22. Savitha MR., *et al*. "Myotonia congenita-A successful response to carbamazepine". *Indian Journal of Pediatrics* 73 (2006): 431-433.

23. Aichele R Aichele., *et al*. "Efficacy of phenytoin, procainamide, and tocainide in murine genetic myotonia". *Experimental Neurology* 87 (1985): 377-381.

24. Conravey A and Santana-Gould L. "Myotonia congenita and myotonic dystrophy: surveillance and management". *Current Treatment Options in Neurology* 12 (2010): 16-28.

25. Bryant SH and Morales-Aguilera A. "Chloride conductance in normal and myotonic muscle fibres and the action of monocarboxylic aromatic acids". *The Journal of Physiology* 219.2 (1971): 367-383.

26. George AL Jr., *et al*. "Molecular basis of Thomsen's disease (autosomal dominant myotonia congenita)". *Nature Genetics* 3.4 (1993): 305-310.

27. Koch MC., *et al*. "The skeletal muscle chloride channel in dominant and recessive human myotonia". *Science* 257.5071 (1992): 797-800.

28. Dunø M., *et al*. "Difference in allelic expression of the CLCN1 gene and the possible influence on the myotonia congenita phenotype". *European Journal of Human Genetics: EJHG* 12.9 (2004): 738-743.

29. Tan SV., *et al*. "Refined exercise testing can aid DNA-based diagnosis in muscle channelopathies". *Annals of Neurology* 69.2 (2011): 328-340.

30. Modoni A., *et al*. "Low-rate repetitive nerve stimulation protocol in an Italian cohort of patients affected by recessive myotonia congenita". *Journal of Clinical Neurophysiology* 28.1 (2011): 39-44.

31. Tang CY and Chen TY. "Physiology and pathophysiology of CLC-1: mechanisms of a chloride channel disease, myotonia". *Journal of Biomedicine and Biotechnology* (2011): 685328.

32. Arzel-Hézode M., *et al*. "Homozygosity for dominant mutations increases severity of muscle channelopathies". *Muscle Nerve* 41.4 (2010): 470-477.

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