A Novel Mutation in the CLCN1 Gene Causing Autosomal Recessive Myotonia Congenita in Siblings

Dear Sir,

Myotonia congenita is the most common inherited skeletal muscle channelopathy, caused by mutations in the chloride channel gene, CLCN1 located on the 7q35 chromosomal region. It is characterized by muscle stiffness during sustained muscle contraction which tends to improve with repeated contraction, which is known as the "warm-up" phenomenon. (1) Both autosomal dominant and recessive forms are known. Several mutations of the CLCN1 gene have been described in different population. Most of them are missense and nonsense mutations, insertions and deletions. Only a few cases of duplications have been described in the literature to date. We report a case of novel duplication in two brothers with a recessive form of myotonic dystrophy.

Two brothers, aged 9 years and 6 years, respectively, presented with a history of stiffness in all limbs and difficulty in walking for a 1-year duration. Stiffness was felt more in lower limbs and was worse during the winter season and getting up. The symptoms were maximal on waking up and improved with after some activity. Over the next 3 months, parents noticed a buildup of muscular arms and legs in both siblings, especially in the younger as compared to the older. They were born to a non-consanguineous marriage and had similar complaints in the family. The children were initially not shown to any physician until the elder brother started to complain of severe colicky pain in the right iliac fossa with nausea and vomiting. The patient was referred to a hospital where after the evaluation was found to have appendicitis and underwent an emergency appendectomy. He was subsequently referred for neurological evaluation along with his younger brother. Neither of them complained of any weakness although both brothers complained of cramping in the calves.

Clinical examination revealed diffuse muscular hypertrophy in all limbs. The eyelashes were long and abundant, there was puckering of the chin with dimpling. Neck height ratio was 1:12. Arm span height ratio was 1:1. Cranial nerves were normal. Muscular hypertrophy was generalized but pronounced in deltoid, biceps, triceps, and supra and infraspinatus group of muscles. Normal muscle strength was noted as assessed with the Medical research council (MRC) sum score. Deep tendon reflexes were attenuated. Sensory and cerebellar examination were within normal limits [Figure 1]. Percussion myotonia was elicited in both the brothers in the hands and tongue. Eyelid myotonia and handgrip myotonia was elicited in both of them.

Serum creatine kinase (CPK-MB) and other laboratory evaluations including blood glucose estimation, renal and kidney function tests, complete hemogram, thyroid and parathyroid hormone levels in both the siblings were within normal limits. Nerve conduction studies were normal and electromyography revealed myotonic discharges in both brothers. A short exercise test revealed a decremental response in compound muscle action potentials (CMAPs) after a sustained contraction of the abductor digiti minimi which repaired within 60 s. Consent for muscle biopsy was denied by parents. Next-generation sequencing of DNA sample revealed a pathogenic mutation in the *CLCN1* gene with sequencing revealing a heterozygous sequence variant (c. 2213dupC; p.L739Sfs*58) in exon12, causing a loss of function of the *CLCN1* gene. This novel mutation was absent in the general population. This mutation was consistent with a clinical diagnosis of myotonia congenita.

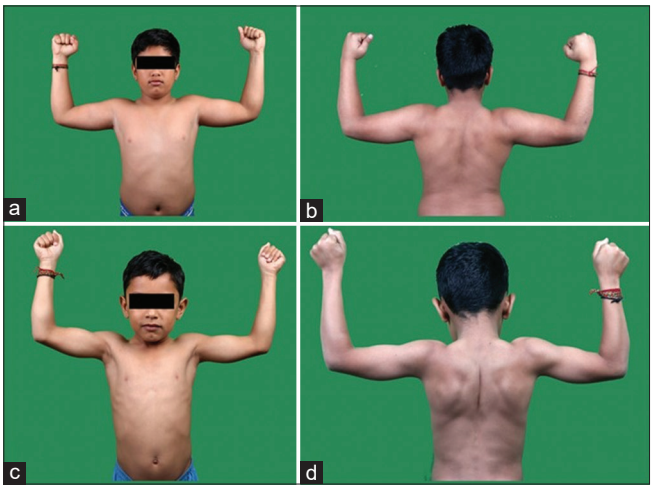

Figure 1: Image showing the muscular hypertrophy of both the brothers. a) and b) show diffuse hypertrophy of biceps, triceps, deltoid, supraspinatus and infraspinatus of the elder brother. c) and d) show marked hypertrophy of the same muscles of the younger brother

Both the brothers were put on sodium channel blocker phenytoin which ameliorated the symptoms in the younger but not the elder brother. He was subsequently put on Mexiletene and responded with significant improvement. Both the parents underwent nerve conduction studies and electromyography, which did not yield any myotonic discharges.

The clinical presentations, absence of family history, and presence of myotonic discharges in electromyography in our patients pointed toward a diagnosis of an autosomal recessive pattern of myotonia congenita. The gene sequencing analysis revealed a novel heterozygous mutation in the CLCN1 gene. The usual presentation of Myotonia congenita is of myotonia that occurs without causing muscular dystrophy and weakness like myotonic dystrophy.[1] However, transient weakness may be seen in some patients. It is usually more prominent in lower limbs than upper limbs, as seen in both the brothers.

The recessive form of myotonia congenita otherwise known as Becker's disease is more common and more severe than its autosomal dominant counterpart, known as Thomsen's disease. The recessive forms of myotonia are usually seen to occur by two loss-of-function mutations in the voltage-dependent chloride channel (CLCN1). On the other hand, Thomsen's myotonia is believed to be caused by a dominant-negative effect. About 150 mutations have been described in the chloride channel causing myotonic congenita, and the phenotype depends on the type and amount of mutations. A subset of CLCN1 mutations has also been found to cause both recessive and dominant forms of MC. Also, heterozygous mutations like seen in our patient can cause only mild myotonia without the presence of significant muscle weakness.[2]

Our patient was found to have a pathogenic mutation in the *CLCN1* gene with a heterozygous mutation in exon 12 (c. 2213dupC: p.L739Sfs*58 causing a loss of function of the *CLCN1* gene. This mutation leads to relative depolarization of the muscle membrane leading to myotonia. Several mutations mainly, missense, non-sense mutations, insertions, deletions have been described in the literature, however, only a few cases of duplication have been described.[3] It is important to check both for duplications and deletions in the chloride channel during genetic analysis for myotonia because hitherto unknown genetic mechanisms may account for the recessive inheritance as well as influence phenotypes of the persons affected. This can also explain the difference in the clinical features of both siblings. The mutation described in our patient has hitherto not been reported in literature and duplication of this gene needs to be added to the growing list of mutations known to cause myotonia in an autosomal recessive fashion.

Gastrointestinal manifestations have been reported in myotonic disorders along with the involvement of many other organ systems.[4] This is because o the involvement of the myenteric plexus in the submucosa of the small intestine in the myotonia in addition to skeletal muscle involvement. Symptoms can vary from difficulty in swallowing to vomiting to intestinal pseudoobstruction or megacolon and can precede the muscle weakness by 15 years.[5] Many times, they have been managed by close monitoring and conservative measures or surgical management in megacolon or obstruction refractory to traditional management. We did not come across the report of any appendicitis in any patient of myotonia congenita. However, we believe that in our case as well, the inflammation of appendicitis could represent the involvement of the myenteric plexus reported in cases of myotonic dystrophy. Recurrent episodes of unexplained intestinal dysmotility or pseudoobstruction syndromes should prompt the clinician to go for a thorough examination of the children, especially for myotonia. However, the genetic mutations observed in our case should not be correlated to the presentation of appendicitis in our patient owing to the high prevalence of these complications in general population itself.

To conclude, this was a novel hitherto unreported mutation in the CLCN1 gene, causing an autosomal recessive variety of myotonia congenita in two siblings. Appendicitis may be a rare manifestation in cases with myotonia congenita but the strength of the association needs to be proven in larger studies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Kamalesh Chakravarty, Vivek Lal, Sucharita Ray

Department of Neurology, PGIMER, Chandigarh, India

Address for correspondence: Dr. Sucharita Ray, Department of Neurology, PGIMER, Chandigarh, India.
E-mail: sucharita.pgi@gmail.com

References

1. Chrestian N, Puymirat J, Bouchard J-P, Dupré N. Myotonia congenita—A cause of muscle weakness and stiffness. Nat Clin Pract Neurol 2006;2:393-9.
2. Dunø M, Colding-Jørgensen E, Grunnet M, Jespersen T, Vissing J, Schwartz M. Difference in allelic expression of the CLCN1 gene and the possible influence on the myotonia congenita phenotype. Eur J Hum Genet 2004;12:738-43.
3. Raja Rayan DL, Haworth A, Sud R, Matthews E, Fialho D, Burge J, *et al*. A new explanation for recessive myotonia congenita: Exon deletions and duplications in CLCN1. Neurology 2012;78:1953-8.
4. Bujanda L, López de Munain A, Alcón A, Gutiérrez Stampa MA, Martínez Pérez-Balsa A, Arenas JI. [The gastrointestinal changes in dystrophia myotonica]. Rev Esp Enferm Dig 1997;89:711-4.
5. Brunner HG, Hamel BC, Rieu P, Höweler CJ, Peters FT. Intestinal pseudo-obstruction in myotonic dystrophy. J Med Genet 1992;29:791-3.

Submitted: 14-Sep-2020 **Revised:** 24-Sep-2020 **Accepted:** 11-Oct-2020
Published: 28-May-2021

DOI: 10.4103/aian.AIAN_970_20