Nondystrophic Myotonic Disorders: Cases From India

Sir,

The nondystrophic myotonias (NDM) are pure skeletal muscle diseases without systemic involvement. They are ion channel disorders caused by mutations in the chloride (CLCN1) or sodium channel (SCN4A) genes with exclusive expression in skeletal muscle [Figure 1]. These mutations may induce depolarization of skeletal muscle cell membrane which leads to hyperexcitability. Their prevalence is estimated at ~1/100000 with higher rates (7-9/100000) in Northern Finland and Norway.\(^{1-3}\) CLCN1 mutations are most common form of NDM (0.52/100000) followed by paramyotonia congenita (0.17/100000) in England study.\(^{21}\) We describe two families with NDM.

Case 1: A 14-year-old boy born of consanguineous marriage complained of stiffness in legs on gait initiation/getting up from squatting posture since last 10 years and difficulty in releasing hand grip for 10 years. On examination, there was generalized muscular hypertrophy [Figure 2a and b]. There was action/percussion myotonia in tongue, muscles of upper and lower limbs with eyelid myotonia. His younger sister had similar features in milder form [Figure 3a]. Electromyography (EMG) showed typical myotonic discharges with classical dive-bomber’s sound. Genetic analysis showed homozygous 5’ splice site variation in intron 12 of CLCN1 gene affecting the invariant GT donor splice site of exon 12 confirming diagnosis of Becker’s myotonia congenita (MC). He had significant improvement with Phenytoin.

Case 2: A 17-year-old boy born of consanguineous marriage presented with difficulty in opening eyes and releasing hand grip since 2 years of age. The symptoms aggravated in cold and on repeated attempts. Since age of 2 years, he experienced recurrent (1–4 every week) attack of rapidly evolving quadriparesis with recovery within 2–3 hours to 1–2 days. Three generations were affected suggesting autosomal dominant inheritance [Figure 3b]. There was eyelid myotonia which worsened with repeated closure [Figure 2c and d] and grip myotonia worsening in cold, followed by weakness lasting for 15–20 minutes. He had percussion and action myotonia. EMG showed diffuse myotonic discharges initially worsening with cooling followed by electrical silence with progressive cooling. With exercise testing, there was significant decrement in compound muscle action...
Serum potassium was 3.5 meq/l. Genetic analysis showed heterozygous missense variation in exon 13 of SCN4A gene which confirmed diagnosis of paramyotonia congenita (PMC). He had significant improvement with mexiletine.

Sir, the genetic analysis in case 1 showed a homozygous 5’ splice site variation in intron 12 of the CLCN1 gene (chr7: g.143029967G >T; Depth: 103x) that affects the invariant GT donor splice site of exon 12 (c. 1401 + 1G >T). The variant has not been reported in the 1000 genomes and internal Indian Population databases and has a minor allele frequency of 0.001% in the ExAC database. The in silico prediction of the variant is damaging by MutationTaster2. The reference base is conserved across species. Till date, several mutations of CLCN1 gene such as missense and nonsense mutations have been reported in different populations. Very few studies have
reported splicing mutations. The observed variation has previously been reported as a compound heterozygous variant (c.1401 + 1G > T and c.1657A > T) in a patient affected with autosomal recessive myotonia congenita. This homozygous splice site mutation in CLCN1 is first ever detected in India.

Mutation in SCN4 cause defects in sodium channel deactivation and fast inactivation. Because of poor inactivation, mild depolarization results in myotonia while severe depolarization causes weakness. PMC is autosomal dominant disorder characterized by myotonia which worsens with exercise, particularly in cold temperatures (paramyotonia). Some patients may report flaccid weakness after exercising in cold environment.

Evidence of myotonia is sought with EMG, whereas evidence of membrane inexcitability (drop in CMAP) is investigated with long and short exercise testing. EMG shows myotonic discharges with a waxing and waning of both amplitude and frequency producing a characteristic audio profile of dive-bomber, or an accelerating and decelerating motorcycle engine. In the “short” exercise test the patient is asked to exercise briefly (10–30 seconds). Post exercise CMAP compared with the CMAP recorded prior to exercise. In PMC, decrement persists for 60 seconds and increases with subsequent trials.

In the “long” exercise test, the CMAP is tested over a 30–45 minutes period following 5 minutes of sustained exercise. In PMC, there is a rapid decline in CMAP amplitude followed by a slow increase back to baseline over next 60 minutes. In hyperkalemic periodic paralysis (HyperKPP), the amplitude increases immediately after exercise and then declines slowly over the course of 15–30 minutes. This distinguishes PMC from HyperKPP. In cooling test, CMAP is recorded before and after cooling the limb for 15–30 min at 15°C. The CMAP decrement in PMC is typically greater than 75%. Cooling initially provoked myotonia in our patient, but after prolonged cooling there was electrical silence. Genetic analysis showed heterozygous missense variation in exon 13 of SCN4A gene (chr17:g.62034820A > G, p.Ile693Thr) which confirmed diagnosis of PMC. The observed heterozygous missense variation lies in the S4S5 linker of domain II of SCN4A protein causing shift in the voltage dependent activation of channel.

To conclude, nondystrophic myotonias are rare disorders manageable by activity modifications, avoiding triggers and pharmacological therapies with excellent prognosis. EMG characteristics of myotonia and paramyotonia greatly aids in neuromuscular diagnosis. During electrodiagnostic studies few additional tests provide correct diagnosis. To the best of our knowledge, homozygous mutation in CLCN1 first ever detected in India.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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