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Case Report

Two Chinese Boys with Non-dystrophic Myotonia: Overview and Experience with Use of Mexiletine and Carbamazepine

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Abstract Non-dystrophic myotonia (NDMs) is a group of heterogenous skeletal muscle channelopathies. This entity is rare but potentially treatable. We reported two children with NDMs, namely myotonia congenita and paramyotonia congenita. The first child presented with abnormal gait with difficulty to initiate movement. The second child had stiffness and gait abnormality precipitated by cold weather. Needle electromyography demonstrated myotonic discharges in both cases. Diagnosis was confirmed by identifying mutations in *CLCN1* and *SCN4A* genes respectively. The first patient had favourable response to treatment with mexiletine. The second child had mild symptoms controlled with *pro re nata* carbamazepine.

Key words Mexiletine; Myotonia congenita; Myotonia; Non-dystrophic myotonia; Paramyotonia

Case Reports

Case 1

A 9-year-old Chinese boy presented with 'abnormal gait' since age of 2, with difficulty in walking upstairs and was described as having 'slow motion' and easy falls. No progressive deterioration was noted. Neurodevelopment was otherwise normal. Physical examination revealed an overweight child with body mass index of 90-97th centile. There was no dysmorphism or myopathic facies. Calf hypertrophy was noted with normal consistency. A wide-based gait was noted with excessive lumbar lordosis. Gower sign was negative. After resting, the child has difficulty in initiating movement with marked stiffness. After repeated exercise, the stiffness resolved gradually, suggesting a 'warm up' phenomenon. Handgrip myotonia was demonstrated. Neurological examination of four limbs, cranial nerves and systemic examination were unremarkable.

Complete blood picture, creatine kinase, liver, renal and thyroid function were unremarkable. Urine metabolic screening was normal. Needle electromyography (EMG) at quadriceps and tibialis anterior muscles showed characteristic 'dive bomber' myotonic discharges, and no myopathic features were noted. Genetic study by Sanger sequencing showed a heterozygous variant of NM_000083.2:c.1876C>T (p.Arg626*) in *CLCN1* (rs201894078; CM1210486), which is a known disease-causing nonsense variant[1] predicted to cause premature truncation of the protein, with normal pattern on multiplex ligation-dependent probe amplification, confirming the diagnosis of autosomal dominant myotonia congenita (MC, MIM#160800) or Thomsen disease. The father, who also had calf hypertrophy but no clinical myotonia, also carried the same variant, suggestive of the same disease.

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The patient was started on carbamazepine up to 100 mg twice a day initially, but this was stopped later due to ineffectiveness and lethargy. Mexiletine was initiated and gradually titrated up to a total daily dose of 300 mg (6.6 mg/kg/day). Parents reported that the child has improved strength when walking upstairs and less clumsiness and stiffness on initiation of movement. There was no significant delay to release hand grip after maximum voluntary contraction, with improved smoothness and reduced time needed to perform repetitive movements (e.g. opening the fist 10 times). Regular monitoring of liver function and QT interval was performed and results were unremarkable. No adverse effects had been documented.

Case 2

An 8-year-old Chinese boy with normal development complained of recurrent episodic limb pain over thigh and calf muscles with stiffness and gait disturbance for 2 years. Each episode lasted up to days and was usually triggered by cold weather. During attacks the child would walk very slowly with stiffness of lower limbs, described by mother as "dragging his legs". Facial stiffness also occurred at times. There was no history of haematuria or dyskinesia. His mother, maternal grandmother, maternal aunt and cousin also experienced similar episodic muscle stiffness during cold weather back in their hometown in Sichuan. The mother's symptoms remitted after she moved to Hong Kong. Physical examination revealed normal growth and gait at room temperature. Power was full in the four extremities. Calf muscles were prominent. No 'warm up' phenomenon or clinical myotonia was noted. Systemic examination was unremarkable. Creatine kinase was moderately elevated to 340 U/L (normal reference: 5 to 205 U/L) without myoglobinuria. EMG at quadriceps and tibialis anterior muscles showed myotonic discharges without myopathic features. Genetic study by Sanger sequencing confirmed a novel heterozygous missense variant NM_000334.4:c.4457G>T (p.Gly1486Val) in a highly conserved residue in *SCN4A*. The mother also carried the same variant. The variant was absent from controls in the Genome Aggregation Database and was predicted to be damaging (MetaSVM/SIFT/PROVEAN) or possibly damaging (Polyphen-2) by *in silico* analyses. Based on the presence of dramatic cold-sensitivity, he was diagnosed as paramyotonia congenita (PMC, MIM#168300), with differential diagnosis of sodium channel myotonia (SCM), a condition with variable cold sensitivity, also dominantly inherited and associated with *SCN4A* mutations. He was put on *pro re nata* low dose carbamazepine. On follow-up he did not report any relapse that required medication intake. He defaulted further follow-up, precluding short-exercise testing to differentiate between the two subtypes, and further family screening and genetic study in other affected family members.

Discussion

Myotonia occurs in many medical conditions (Table 1).[2] Non-dystrophic myotonia (NDM) belongs to a group of skeletal channelopathies resulting in muscle hyperexcitability without progressive weakness. NDM encompasses MC, PMC and SCM, with an estimated prevalence of 1 in 100,000.[3] It can be distinguished from myotonic dystrophy by the absence of systemic manifestations.

MC is caused by mutation in voltage- gated chloride channel gene (*CLCN1,* MIM*118425) on chromosome 7q34, and can be inherited in autosomal dominant (Thomsen) and autosomal recessive (Becker) manners.[3] Thomsen disease is more common in Chinese (86.1%), while the recessive form is more common in the West.[4] Mutation in *CLCN1* gene leads to reduction in chloride conductance, with resultant muscle membrane hyperexcitability.[3] A characteristic clinical feature is the 'warm up' phenomenon evident by significant muscle stiffness following a period of rest which improves with repeated exertion, identified in up to 95% of patients.[3,4] Other features include muscle hypertrophy and episodic muscle weakness, which are more prominent in recessive form.[3] Becker disease is also distinguished by later age of onset, more severe myotonia with lower limb involvement and depressed deep tendon reflexes.[3]

In PMC, an autosomal dominant condition caused by *SCN4A* (MIM*603967) mutation on 17q23.3 affecting sodium channel, the key feature is aggravation of myotonia by cold temperature which helps to distinguish it from other NDM.[3] 'Paradoxical' myotonia is another characteristic in PMC in which muscle stiffness tends to be worsen by exertion, unlike in MC.[3] Myotonia predominantly affects hands and face with eyelid myotonia, and can persist up to hours or days. Muscle hypertrophy is less common.[3]

While the subtypes of NDM is primarily classified by specific clinical manifestations and demonstration of electrical myotonia with and without clinical myotonia, in non-specific cases specialised neurophysiological protocols can help direct target genetic testing by demonstration of channel-specific electrophysiological patterns.[3] In the short

exercise protocol, supramaximal stimulation is applied to the ulnar nerve at the wrist and compound muscle action potential (CMAPs) are recorded at the abductor digiti minimi (ADM) at baseline. CMAP is measured again after 10 seconds of sustained ADM contraction, 2 seconds post-exercise, then every 10 seconds till 60 seconds post-exercise.[5] The protocol should be repeated 3 times and sensitivity can be improved by limb cooling to 20-25 degrees Celsius.[5] Decrements of 19% to 40% less than pre-exercise baseline CMAP amplitude are abnormal.[5] Table 2 lists the characteristic patterns in different types of NDMs.[3] Target gene analysis may then be conducted to differentiate the specific type of NMD.

Pharmacological treatment is only indicated in severe cases with functional impairment.[3] In 2012, mexiletine was found to be effective in reducing patient-reported stiffness and handgrip myotonia in a randomised placebo-controlled trial involving 59 NMD patients.[6] It was mentioned that mexiletine acts on voltage-gated sodium channel to stop the production of repetitive action potentials. Recommended dosage ranges from 1 mg/kg/day up to 8 mg/kg/day.[7] From our experience, it takes up to a few months to a year before clinical improvement can be seen. It is usually well tolerated. Side effects include gastrointestinal discomfort (20%) and lightheadedness (10%), liver function derangement, blurred vision and tremor.[7] As it is proarrhythmic,[3] mexiletine is

Table 1 Differential diagnosis of electrical myotonia[2,5]

Clinical conditions	Subtypes	Electrical myotonia	Clinical myotonia
Muscular dystrophy	Myotonic dystrophy type 1 and 2 Myofibrillar myopathy	+	+
Congenital myopathy	Centronuclear myopathy Nemaline myopathy Congenital fibre type disproportion	+	–
Skeletal muscle channelopathies	Non dystrophic myotonia Hyperkalemic periodic paralysis	+	+
Metabolic	Pompe disease McArdle disease Debrancher enzyme deficiency	+	–
Inflammatory myositis	Dermatomyositis Polymyositis	+	–
Endocrine	Hypothyroidism	+	–
Drug	Statin Colchicine Chloroquine / hydroxychloroquine	+	–

Table 2 Channel-specific electrophysiological patterns in NDMs[3]

	MC (AD)	MC (AR)	Paramyotonia congenita	Sodium channel myotonia
Short exercise test without cooling	Little or no decrement in CMAP	Early decrement in CMAP with quick recovery and diminishes with repetition	Gradual and persistent reduction in CMAP	No significant change of CMAP
Short exercise test with cooling	Early decrement in CMAP with quick recovery and diminishes with repetition may be seen	Cooling – little further effect	Reduction enhanced further by cooling	No significant change

NDMs: Non-dystrophic myotonia; MC: myotonia congenita; AD: autosomal dominant; AR: autosomal recessive; CMAP: compound motor action potential

contraindicated in patients with cardiac arrhythmia, cardiomyopathy or coronary artery disease.[6] Monitoring of liver function and QT interval is mandatory.[3,7]

Sodium channel blockers such as carbamazepine and phenytoin are also commonly used agents with varying effects.[3,7] Acetazolamide, a carbonic anhydrase inhibitor, has also been reported to be beneficial.[3] Class Ic anti-arrhythmics, such as flecainide and propafenone, have potential anti-myotonic effect but are seldom used in clinical practice.[3] Lifestyle modifications including avoidance of cold and stress reduction can help in milder cases.[3]

In NDMs, depolarising muscle relaxants such as suxamethonium should be avoided due to potential worsening of myotonia.[7] Caution should be taken with use of anaesthetic agents due to risk of malignant hyperthermia.[7] While NDMs are generally regarded as benign conditions, painful myotonias and fatigue are reported in a significant number of genetically confirmed patients.[8]

Conclusion

Nondystrophic myotonia is a group of skeletal muscle channelopathies with many overlapping clinical features. Clinical finding of myotonia without progressive deterioration or systemic involvement should raise the suspicion of NDMs. Although rarely seen, this condition can have significant negative impact on daily function. Early recognition and initiation of treatment especially in cases with severe symptoms would greatly improve quality of life.

Declaration of Interest

The authors declare that they have no financial or other conflicts of interest in relation to this publication.

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