Skeletal Muscle Channelopathies: Rare Disorders with Common Pediatric Symptoms

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Objective To ascertain the presenting symptoms of children with skeletal muscle channelopathies to promote early diagnosis and treatment.

Study design Retrospective case review of 38 children with a skeletal muscle channelopathy attending the specialist pediatric neuromuscular service at Great Ormond Street Hospital over a 15-year period.

Results Gait disorder and leg cramps are a frequent presentation of myotonic disorders (19 of 29). Strabismus or extraocular myotonia (9 of 19) and respiratory and/or bulbar symptoms (11 of 19) are common among those with sodium channelopathy. Neonatal hypotonia was observed in periodic paralysis. Scoliosis and/or contractures were demonstrated in 6 of 38 children. School attendance or ability to engage fully in all activities was often limited (25 of 38).

Conclusions Children with skeletal muscle channelopathies frequently display symptoms that are uncommon in adult disease. Any child presenting with abnormal gait, leg cramps, or strabismus, especially if intermittent, should prompt examination for myotonia. Those with sodium channel disease should be monitored for respiratory or bulbar complications. Neonatal hypotonia can herald periodic paralysis. Early diagnosis is essential for children to reach their full educational potential. *(J Pediatr 2017;188:181-5).*

Skeletal muscle channelopathies are rare genetic neuromuscular disorders that include the nondystrophic myotonias[1] and the primary periodic paralyses.[2] Characteristic symptoms are episodic muscle stiffness (myotonia) or muscle paralysis. Causative genes include *CLCN1*[3] (myotonia congenita [MC]), *SCN4A*[4-6] (paramyotonia congenita, sodium channel myotonia, hyperkalemic periodic paralysis (hyperPP), and hypokalemic periodic paralysis), *CACNA1S*[7] (hypokalaemic periodic paralysis), and *KCNJ2*[8] (Andersen-Tawil syndrome [ATS]). The typical phenotype of the muscle channelopathies has been studied and reported in a number of adult cohorts,[9-13] but to our knowledge there is no large cohort study of children, despite disease onset occurring more often in childhood.

In adult series, an average time to diagnosis from onset of first symptoms of 12 to 19 years has been reported,[9,11] with patients seeing an average of 4 different physicians (range 1-10) in 1 series[11] before a diagnosis was made. Erroneous diagnoses included malingering, depression, and functional disorders.[11] The typical age of symptom onset of the channelopathies is in the first or second decade.[1,2] This indicates that in a significant number of children, these symptoms are not addressed at all and these conditions are not considered in the differential diagnosis. What influence this diagnostic delay may have on morbidity or on a child's educational opportunities is largely unknown.

We sought to determine the phenotypic features of individuals with skeletal muscle channelopathies who present in childhood. We aimed to ascertain if they are typical of an adult presentation or if there are specific features that may help to enhance the recognition and treatment of these disorders at an earlier age.

Methods

We undertook a case note review of all children with a diagnosis of skeletal muscle channelopathy seen over 15 years at the Dubowitz neuromuscular service, Great Ormond Street Hospital, London. This review was part of a service evaluation approved by the hospital's audit and governance team.

Genetic analysis was performed at the Neurogenetics Unit, National Hospital for Neurology and Neurosurgery, as provided by the Channelopathy Highly

ATS	Andersen-Tawil syndrome
hyperPP	Hyperkalemic periodic paralysis
hypoPP	Hypokalemic periodic paralysis
MC	Myotonia congenita

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Specialised National Service for rare disease. Samples underwent next-generation sequencing on an Illumina HiSeq after enrichment with an Illumina custom Nextera Rapid Capture panel (Illumina, Inc, San Diego, California) and/or direct Sanger Sequencing and multiplex ligation-dependent probe amplification using methods previously described.[14]

Results

Thirty-eight children were identified whose notes were available for review. Thirty-seven had a genetic diagnosis of skeletal muscle channelopathy. One met all diagnostic criteria for ATS,[15,16] but no mutations or rearrangements were found in the *KCNJ2* gene. It is recognized that there is a significant proportion of patients with this phenotype who are *KCNJ2* negative[8] and therefore this child was also included in the analysis because a clinical diagnosis of channelopathy was considered highly probable.

The most common diagnosis was of nondystrophic myotonia, 19 with paramyotonia congenita or sodium channel myotonia, and 10 with MC. Periodic paralysis was confirmed in 7, 4 with hyperPP, 2 with hypokalemic periodic paralysis (hypoPP), and 1 with potassium-sensitive normokalemic periodic paralysis. ATS was the rarest with only 2 cases identified (including the *KCNJ2*-negative case). In 24 of the 38 cases (63%), there was an established family history of channelopathy.

Many features in our cohort were similar to those described among adult cohorts, including age at onset, distribution of muscle symptoms, muscle hypertrophy (**Figure 1**; available at www.jpeds.com), and exacerbating and relieving factors (**Table**; available at www.jpeds.com). A number of features seen in our cohort, however, have not been recognized previously as a typical feature of channelopathy. Others are rarely reported in adults, but were relatively common in our pediatric population.

Of the 19 cases of *SCN4A*-related myotonia, the most common presentation was with limb (legs and hands) myotonia 10 of the 19 (53%). Leg myotonia was often described or manifested as limited exercise tolerance, "funny gait," falls, or leg cramps (9 of 19). Either eyelid or extraocular myotonia was the first symptom noted by parents or the presenting symptom in 7 of 19 cases (37%). The remaining 2 (10%) presented with stridor or gasping and choking episodes. All of the MC cases (10 of 10) presented with symptoms of leg myotonia manifesting as a combination of below average running and/or skipping ability compared with peers, frequent falls, or a "funny gait" described by parents or other referring clinicians. One of these MC cases was referred to us with gait abnormality and mildly elevated creatine kinase (350 units; upper limit of laboratory reference range 205 units) with an initial presumed diagnosis of muscular dystrophy.

In the periodic paralyses, all the hyperPP cases presented with recurrent episodes of muscle weakness and "floppiness," although 2 sisters had also been noted to have neonatal hypotonia. Their mother, who also has hyperPP, reported knowing "from birth" they were affected because of the hypotonia. The hypoPP cases presented at a typical age of onset in the early teens, waking at night with quadraparesis. The 1 child with potassium-sensitive normokalemic periodic paralysis had attacks of paralysis similar to hypoPP in that they were very long, lasting hours to days, and often occurred at night, but her age of onset was earlier at 2 years.

Cardiac disease was the predominant presenting feature in both ATS cases, one diagnosed incidentally owing to abnormal electrocardiogram monitoring during appendectomy and one owing to recurrent episodes of loss of consciousness (owing to ventricular tachycardia). In retrospect, both children had exhibited an earlier history with cleft palate, short stature, slow running in one compared with peers, and in the other dental abnormalities and parental concerns over a small jaw and small hands. Neither was described to have any episodes of frank paralysis, although they did report episodes of limb weakness.

Five children were observed to have contractures (Achilles tendons or elbows), 3 of whom had MC, 1 sodium channel-related myotonia, and 1 periodic paralysis. The Achilles tendon shortening was managed by stretching exercise and ankle–foot orthoses. In addition, 1 of these children with severe myotonia despite treatment with mexiletine developed scoliosis from age 8. This scoliosis was progressive and required surgical intervention at age 16 (**Figure 2**). An additional child with ATS was also noted to have scoliosis.

Strabismus and/or diplopia (or "blurred" vision) was only reported by children with *SCN4A*-related myotonia (9 of 19 cases; 47%) and was the presenting symptom in 7 of these. Symptoms were intermittent or, in the case of strabismus, often of variable angle but 1 child did ultimately require surgical correction with a good outcome.

Significant respiratory and/or bulbar symptoms were most commonly seen in *SCN4A*-related myotonia (11 of 19; 60%), although it should be noted that 1 child had an additional diagnosis of cerebral palsy and 1 case may be unrelated to the myotonic disorder because symptoms resolved after adenotonsillectomy. These symptoms were described across numerous *SCN4A* mutations (**Table**), but were reported consistently by those with the V1589M mutation. Severity was variable and episodes of children "turning blue" and on 1 occasion "passing out" were reported, suggesting significant respiratory compromise could occur. Other minor symptoms included jaw myotonia limiting swallowing in 1 child with MC and breathlessness and difficulty swallowing during an attack of hypoPP in another.

Twenty-five children required either modifications at school or had difficulty getting to school. Support was often required in regard to extra time or help to write, especially during time-limited examinations and maneuvering stairs between lessons. There were frequent concerns over missing or needing to modify physical activity or games and the impact this may have on social interaction. Missed attendance at school was more common in the periodic paralyses with approximately 50% of children reporting attacks that would leave them too weak to attend.