Skeletal muscle channelopathies: rare disorders with common pediatric symptoms

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Abstract

Objective: To ascertain the presenting symptoms of children with skeletal muscle channelopathies in order to promote early diagnosis and treatment. Skeletal muscle channelopathies are genetic disorders but no large cohort studies exist for affected children. It is largely unknown if presenting features differ between children and adults. Average time to diagnosis from first symptom reported by adults is 12 to 19 years. As symptom onset is usually before age twenty, there is a missed opportunity to recognise, diagnose and treat many of these patients in childhood. This may cause significant morbidity and limit educational potential.

Study design: Retrospective case note review of 38 children with a skeletal muscle channelopathy attending the specialist paediatric 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 (19/29). Strabismus/extra-ocular myotonia (9/19), respiratory and/or bulbar symptoms (11/19) are common among those with sodium channelopathy. Neonatal hypotonia was observed in periodic paralysis. Scoliosis and/or contractures were demonstrated in 6/38 children. School attendance or ability to fully engage in all activities was often limited (25/38).

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/bulbar complications. Neonatal hypotonia is important to consider in birth planning. Early diagnosis is essential for children to reach their full educational potential.

Introduction

Skeletal muscle channelopathies are rare genetic neuromuscular disorders that include the non-dystrophic 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), SCN4A (4-6) (paramyotonia congenita, sodium channel myotonia, hyperkalemic periodic paralysis and hypokalaemic periodic paralysis), CACNA1S (7) (hypokalaemic periodic paralysis) and KCNJ2 (8) (Andersen-Tawil syndrome). 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 in children despite these being mostly childhood onset disorders.

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 up to 10) in one series (11) before a diagnosis was made. Erroneous diagnoses included malingering, depression and functional disorders (11).

The typical age of 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 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 Specialised National Service for rare disease. Samples underwent Next-Generation Sequencing on an Illumina HiSeq following enrichment with an Illumina custom Nextera Rapid Capture panel (Illumina, Inc., San Diego, CA) and/or direct Sanger Sequencing and MLPA 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 Andersen-Tawil Syndrome (ATS) (15;16) but no mutations or re-arrangements were found in the KCNJ2 gene. It is recognised 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 as a clinical diagnosis of channelopathy was considered highly probable.

The most common diagnosis was of non-dystrophic myotonia, nineteen with paramyotonia congenita (PMC) or sodium channel myotonia (SCM) and ten with myotonia congenita (MC). Periodic paralysis was confirmed in seven, four with hyperkalemic periodic paralysis (hyperPP), two with hypokalemic periodic paralysis (hypoPP) and one with potassium sensitive normokalemic periodic paralysis. Andersen-Tawil syndrome was the rarest with

only two cases identified (including the KCNJ2 negative case). In 24/38 cases (63%) there was an established family history of channelopathy.

Many features were similar in our cohort to those described among adult cohorts including age at onset, distribution of muscle symptoms, muscle hypertrophy (see Fig 1 online only), exacerbating and relieving factors (see Table 1 online only). A number of features seen in our cohort however have not been previously recognised as a typical feature of channelopathy. Others are rarely reported in adults but were relatively common in our paediatric population.

First symptoms

Of the 19 cases of SCN4A related myotonia, the most common presentation was with limb (legs and hands) myotonia 10/19 (53%). Leg myotonia was often described or manifested as limited exercise tolerance, “funny gait”, falls or leg cramps (9/19). Either eyelid or extra-ocular myotonia was the first symptom noted by parents or the presenting symptom in 7/19 (37%) cases. The remaining two (10%) presented with stridor or gasping and choking episodes. All of the myotonia congenita cases, 10/10 (100%) presented with symptoms of leg myotonia manifesting as a combination of below average running and/or skipping ability compared to peers, frequent falls or a “funny gait” described by parents or other referring clinicians. One of these myotonia congenita cases was referred to us with gait abnormality and mildly elevated CK (350 units – upper limit of lab reference range 205units) 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 two sisters had also been noted to have neonatal hypotonia. Their mother who also has hyperPP reports knowing “from birth” they were

affected because of this. The hypoPP cases presented at a typical age of onset in the early teens waking at night with quadriparesis. The one 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 due to abnormal ECG monitoring during appendectomy and one due to recurrent episodes of loss of consciousness (due to ventricular tachycardia). In retrospect both children had an earlier history with cleft palate, short stature and being slower than peers when running in one and the other having dental abnormalities and parental concerns over a small jaw and small hands. Neither described any episodes of frank paralysis although did report episodes of limb weakness.

Contractures and Scoliosis

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

Strabismus and diplopia

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

Respiratory and bulbar symptoms

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

Schooling

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 manoeuvring 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.

Time to diagnosis

Fifty percent of the children were diagnosed clinically as having a skeletal muscle channelopathy within two years of their first symptom, and the majority of these within 6 months (see Fig 3). The remaining fifty percent waited between three and thirteen years. One child underwent a muscle biopsy without any documented evidence of myotonia being sought on clinical examination. When he was examined at the neuromuscular clinic, myotonia was easily elicited. All children were given a clinical diagnosis of skeletal muscle channelopathy based on clinical history and examination at their first visit to the specialist neuromuscular clinic.

The reasons for delay to diagnosis were variable and our retrospective study was not ideal to quantify this. In some cases it was evident parents had sought help from the general practitioner or other hospital specialists on several occasions before being referred to the neuromuscular clinic. In others however, affected parents identified their child was symptomatic at a young age but delayed seeking medical input until they felt treatment may be warranted. This often coincided with their child wanting to play sports or transferring to secondary school.

Discussion

Our study highlights a number of important clinical observations that are useful for recognition and management of morbidity in children with skeletal muscle channelopathies.

Neonatal hypotonia was reported in two sisters with hperPP associated with the SCN4A T704M mutation. We have previously reported neonatal hypotonia and variable feeding and respiratory difficulties in four families with paramyotonia congenita carrying the SCN4A I693T mutation(17) but it has not been recognised as a feature of periodic paralysis. The child with the I693S mutation in our cohort did not report neonatal hypotonia but did have episodes of noisy or wheezy breathing induced by cold drinks (see Table 1 online only). A child with I693L mutation and more significant episodes of respiratory compromise has also been reported (18) supporting a possible genotype-phenotype correlation for mutations at this residue and respiratory compromise. Our cases of neonatal hypotonia with the T704M hyperPP mutation suggest neonatal hypotonia however may be a more widespread phenomenon among infants with SCN4A related phenotypes. Expectant mothers and their obstetric team need to be counselled about this possibility so that appropriate birth planning can take place and unnecessary investigation avoided.

Presenting symptoms in our cohort reflect a predominance of myotonia in the leg muscles for those with chloride channel myotonia and for the eyes (eyelids and extra-ocular muscles) in those with sodium channel disease. A differential distribution of myotonia between the two disorders, legs in chloride channel and eyelids in sodium channel is reported in adults but extra-ocular myotonia has not been widely recognised (19;20). In two large adult series extra-ocular myotonia was not identified at all (9;10). It is our clinical experience from the national referral centre for muscle channelopathies in the UK that extra-ocular myotonia does occur in adults with sodium channel myotonic disorders but is rarely troublesome and usually has to be specifically asked for in the history. However, this paediatric cohort suggests it is a more significant and common phenomenon in children.

There also appears to be a difference in the way presenting myotonic symptoms are characterised between adults and children. All of the children with chloride channel disease manifested as a gait disorder or poor motor ability compared to peers with frequent falls. Leg cramps were commonly described but the stimulus for referral tended to be the gait and mobility symptoms. Adults usually report “stiffness” as their most common symptom (9;10). One child even underwent a muscle biopsy for presumed muscular dystrophy before myotonia was sought and demonstrated on clinical examination. Leg cramps are a very common symptom in childhood and often benign but a clinical examination for myotonia and muscle hypertrophy is quick and easy to perform. These data suggest that all children with symptomatic leg cramps or unusual gait should be examined for the presence of myotonia as this could avoid invasive and unnecessary investigation.

Limb contractures or Achilles tendon tightening were identified in five children, four with myotonia and one with periodic paralysis. In addition one child with myotonia congenita had a severe scoliosis requiring surgery and one child with ATS had scoliosis. To our knowledge contractures have only been reported once previously in a child with SCN4A related myotonia (21) and scoliosis not at all in the myotonic disorders, although it is recognised in ATS (13). Our findings suggest these may be under-recognised features of skeletal muscle channelopathies.

Symptomatic respiratory and/or bulbar compromise is very rarely reported in adults with muscle channelopathies (1) but was common amongst our paediatric cohort. In general respiratory or bulbar symptoms were most common and most severe in those with SCN4A related myotonia (60% of cases) particularly those with the V1589M SCN4A mutation (present in 100% of cases although one did resolve following tonsillectomy). One of the rare adult cases reported describes cold induced oropharyngeal myotonia and stridor in a

woman carrying the SCN4A V1589M mutation (22). This suggests a genotype-phenotype correlation may exist with the V1589M mutation and bulbar/respiratory myotonia.

A severe form of life-threatening infantile SCN4A myotonia affecting the larynx and respiratory muscles has been reported in a handful of cases and is considered very rare (23-27). Our cohort indicates myotonia of these muscles is actually very common in children carrying SCN4A mutations although the severity clearly varies. Overall this has important implications for monitoring infants and children with SCN4A mutations and potentially particularly those carrying the V1589M mutation and mutations at the I693 residue.

Our study highlights a number of important differences in common presenting symptoms between children and adults with skeletal muscle channelopathies. We propose all children presenting with “funny gait”, leg cramps, diplopia or variable strabismus should be examined for the presence of myotonia. Respiratory and bulbar compromise of variable severity is common amongst those with SCN4A related myotonic disorders. Children with SCN4A mutations or neonates at risk of having inherited them should be monitored for these complications. Expectant mothers who either carry an SCN4A mutation themselves or whose partner does should additionally be counselled regarding the possibility of neonatal hypotonia should their child inherit the mutation. The ability to attend or engage in all school activities or work is commonly limited in children with channelopathies and an accurate diagnosis is imperative to limit physical and psychological morbidity and ensure they achieve their full educational potential.

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Figure Legends

Figure 1 online only: biceps hypertrophy in a child with myotonia congenita

Figure 2: progressive scoliosis in a child with myotonia congenita, A: age 8 years, B: age 16 years, C: age 16 years post-scoliosis surgery

Figure 3: bar graph depicting the time taken to achieve a clinical diagnosis of channelopathy after the onset of first symptoms

Abbreviations

MC myotonia congenita

SCM sodium channel myotonia

PMC paramyotonia congenita

ATS Andersen-Tawil syndrome