Stridor expands the neonatal presentations of skeletal muscle sodium channelopathy

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Abstract

Objectives: To describe stridor as the presenting feature of a neonate affected by the skeletal muscle sodium channelopathy paramyotonia congenita.

Design: Case report

Settings: Out-patient neuromuscular clinics at Great Ormond Street Hospital for Children and the MRC Centre for Neuromuscular Disease at the National Hospital for Neurology and Neurosurgery, Queen Square, London.

Patient: A child carrying the T1313M SCN4A mutation associated with paramyotonia congenita.

Intervention: Supportive care in the neonatal period. Mexiletine at age four years.

Main outcome measures: The association of stridor and paramyotonia congenita were made retrospectively following the diagnosis in the infant’s mother. The child is now regularly reviewed at the paediatric out-patient clinic.

Results: Persistent stridor was present for the first six months of life and episodic stridor can still be exacerbated by intercurrent respiratory tract infection, cold, laughter or crying. Common symptoms of paramyotonia congenita have been apparent from age one year and are beginning to respond to a recent trial of mexiletine.

Conclusions: Neonatal stridor has not previously been reported in the skeletal muscle sodium channelopathies. The recognition that infants inheriting mutations known to cause paramyotonia congenita are inherently at risk of developing neonatal complications following an uneventful labour is important for all training neurologists in order to advise expectant mothers and paediatric and obstetric colleagues appropriately.
Paramyotonia congenita is a skeletal muscle sodium channelopathy due to mutations in the SCN4A gene that lead to dysfunction of the voltage gated sodium channel, Nav1.4 and altered sarcolemmal excitability. Clinical symptoms of episodic muscle stiffness (myotonia due to a hyper-excitable membrane) and muscle weakness (an inexcitable membrane) reflect this. Affected mothers are counseled and monitored for the possibility of peri-natal complications such as generalized muscle paralysis or a myotonic crisis that may place the neonate and mother at risk of a prolonged and difficult labour. It is only recently that neonatal presentations varying from hypotonia\textsuperscript{1} to a fatal outcome\textsuperscript{2} have been described and attributed to the presence of an SCN4A mutation in the child themselves irrespective of the mother’s genetic pre-disposition or progress of labour. Here we expand these presentations further by describing neonatal stridor in an infant carrying the T1313M SCN4A mutation associated with paramyotonia congenita.

Case History

A four year old boy was referred to paediatric services following the diagnosis of paramyotonia congenita (PMC) in his mother. The boy was the mother’s second child and was born by vacuum assisted delivery at 39 weeks following an uncomplicated pregnancy. APGAR scores were normal and post natal examination was unremarkable. Within 24 hours of delivery he was transferred to the neonatal intensive care due to inspiratory stridor and poor feeding (see supplemental data for a video of the neonate with dramatic stridor submitted with parental consent). Over the following week he was unable to take sufficient oral feeds and required supplemental nasogastric feeding. Stridor
persisted and he required intermittent oxygen therapy for desaturations that occurred while attempting to bottle feed or when crying. Laryngoscopy showed findings consistent with laryngomalacia.

The infant continued to have persistent inspiratory stridor for the first six months of life. Feeds were prolonged but he gained weight appropriately and had no further apnoeic episodes. Motor milestones were mildly delayed, sitting independently at nine months and walking at 19 months. From the age of one year exotropia was noted. This is currently under investigation by an ophthalmologist and possibly reflects myotonia of the extraocular muscles.

At the age of 23 months he fell in the garden on a cold day and complained of leg weakness, refusing to stand or walk. The weakness recovered spontaneously within five hours. A second similar episode occurred at age 27 months after playing in the garden in winter. In addition to these two episodes of muscle weakness his mother noted muscle stiffness occurring on an almost daily basis from age two. Both muscle stiffness and weakness were exacerbated by cold weather and exertion.

At the age of four he continues to have episodes of inspiratory stridor exacerbated by viral illness, cold weather, and prolonged laughter or crying. A humidifier is helpful in aborting such episodes.

He has recently been treated with the sodium channel blocker mexiletine which has had some beneficial effect on his degree of myotonia and exotropia.
The child’s mother, grandfather and great uncle all reported similar episodes of muscle stiffness and weakness exacerbated by cold and exercise. There was no prior family history of stridor. All affected family members including the child reported have been shown to have the SCN4A mutation T1313M associated with PMC³.

In addition to this case we have identified two further adult cases of PMC in whom neonatal stridor was documented in their medical records although no further details were available. The first carried an E1702K familial mutation, and the other an A444D de novo mutation. (D.Sternberg, S.Vicart, personal communication).

Discussion
Paramyotonia congenita is a dominantly inherited neuromuscular disorder caused by mutations in the SCN4A gene that encodes the alpha sub-unit of the skeletal muscle voltage gated sodium channel. These mutations result in altered skeletal muscle membrane excitability. SCN4A is expressed in all skeletal muscles including those in the larynx. Typically PMC presents in the first decade with cold and exercise induced episodic muscle stiffness (myotonia) and muscle weakness, predominantly affecting the muscles of the face and upper limbs.

Hypokalaemic periodic paralysis (HyperPP) is a dominantly inherited disorder which is allelic to PMC and is characterised by episodes of muscle weakness and myotonia, although weakness is the predominant symptom. In both disorders mutations result in “gain of function” sodium channel defects. It has been proposed that the two disorders reflect ends of a spectrum of the same disease.⁴
Stridor has been described in patients with myotonic dystrophy, in both neonates and adults.\textsuperscript{5,6} In addition there are several reports of stridor in American Quarter horses affected by the equine form of hyperkalaemic periodic paralysis (HyperPP). In one series 63/68 affected horses suffered stridor in association with exertion, muscle weakness or excitement.\textsuperscript{7} There is also one case report of an adult with PMC in whom provocative testing with muscle cooling induced severe laryngeal myotonia with stridor.\textsuperscript{8}

We suggest that it is likely the stridor reflects myotonia of the laryngeal muscles. In addition the child presented here experienced feeding and respiratory difficulties which we also noted in our previously reported cases of hypotonia\textsuperscript{1} suggesting these are common neonatal features of PMC. Dysphagia and respiratory compromise are rarely reported in adult cases.

The present cases of neonatal stridor add to our recent report of neonatal hypotonia with the PMC sodium channel mutation I693T\textsuperscript{1}. Taken together these observations indicate that offspring of parents with sodium channel mutations are at risk of neonatal complications. \textbf{Whilst idiopathic causes of stridor are not excluded in these infants} we suggest that treating neurologists should be aware of the possibility of laryngeal myotonia and the other complications described in order to counsel mothers and to avoid unnecessary investigations of affected neonates.
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Supplemental Video Caption

File Format: mpg

Title: Neonatal stridor

Content: Short clip of neonate carrying the T1313M SCN4A mutation associated with paramyotonia congenita with severe inspiratory stridor.
Reference List


