

# Stridor as a Neonatal Presentation of Skeletal Muscle Sodium Channelopathy

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**Objective:** To describe stridor as the presenting feature in a neonate with the skeletal muscle sodium channelopathy paramyotonia congenita.

**Design:** Case report.

**Setting:** Outpatient neuromuscular clinics at Great Ormond Street Hospital for Children and the Medical Research Council Centre for Neuromuscular Disease at the National Hospital for Neurology and Neurosurgery, London, England.

**Patient:** A child carrying the Thr1313Met *SCN4A* mutation associated with paramyotonia congenita.

**Intervention:** Supportive care in the neonatal period and administration of mexiletine hydrochloride at age 4 years.

**Main Outcome Measure:** The association of stridor and paramyotonia congenita was made retrospectively

following the diagnosis in the infant's mother; the child is now regularly reviewed at the pediatric outpatient clinic.

**Results:** Persistent stridor was present for the first 6 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 1 year and are beginning to respond to a recent trial of mexiletine.

**Conclusions:** To our knowledge, neonatal stridor has not previously been reported in skeletal muscle sodium channelopathies. The recognition that infants inheriting mutations known to cause paramyotonia congenita are inherently at risk for developing neonatal complications following an uneventful labor is important for all training neurologists so they can advise expectant mothers and pediatric and obstetric colleagues appropriately.

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**P**ARAMYOTONIA CONGENITA (PMC) is a skeletal muscle sodium channelopathy due to mutations in the *SCN4A* gene (GenBank AAO83647) that lead to dysfunction of the voltage-gated sodium channel Nav1.4 and altered sarcolemmal excitability. Clinical

varying from hypotonia<sup>1</sup> to a fatal outcome<sup>2</sup> have only recently been described and attributed to the presence of an *SCN4A* mutation in the child irrespective of the mother's genetic predisposition or progress of labor. Herein, we expand these presentations further by describing neonatal stridor in an infant carrying the Thr1313Met *SCN4A* mutation associated with PMC.

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symptoms of episodic muscle stiffness (myotonia due to a hyperexcitable membrane) and muscle weakness (an inexcitable membrane) reflect this. Affected mothers are counseled and monitored for the possibility of perinatal complications such as generalized muscle paralysis or a myotonic crisis that may place the neonate and mother at risk for a prolonged and difficult labor. Neonatal presentations

## REPORT OF A CASE

A 4-year-old boy was referred to pediatric services following the diagnosis of PMC in his mother. He was the mother's second child and was born by vacuum-assisted delivery at 39 weeks following an uncomplicated pregnancy. The Apgar scores were normal and postnatal examination results were unremarkable. Within 24 hours of delivery, he was transferred to the neonatal intensive care unit owing to inspiratory stri-

dor and poor feeding (a video shows the neonate with dramatic stridor, <http://www.archneuro.com>). During the following week, he was unable to take sufficient oral feedings 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 6 months of life. Feedings were prolonged, but he gained weight appropriately and had no further apneic episodes. Motor milestones were mildly delayed, with the boy sitting independently at age 9 months and walking at age 19 months. From age 1 year, exotropia was noted. This is currently under investigation by an ophthalmologist and possibly reflects myotonia of the extraocular muscles.

At age 23 months, the boy fell in the garden on a cold day and reported leg weakness, refusing to stand or walk. The weakness recovered spontaneously within 5 hours. A second similar episode occurred at age 27 months after playing in the garden in winter. In addition to these 2 episodes of muscle weakness, his mother noted muscle stiffness occurring on an almost daily basis from age 2 years. Both muscle stiffness and weakness were exacerbated by cold weather and exertion.

At age 4 years, 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 hydrochloride, which has had some beneficial effect on his degree of myotonia and exotropia.

The child's mother, grandfather, and great uncle reported similar episodes of muscle stiffness and weakness exacerbated by cold and exercise. There was no family history of stridor. All affected family members, including our patient, have been shown to have the *SCN4A* mutation Thr1313Met associated with PMC.<sup>3</sup>

In addition to this case, we have identified 2 other adults with PMC in whom neonatal stridor was documented in their medical records, although no further details were available. The first patient carried a Glu1702Lys familial mutation, and the other carried an Ala444Asp de novo mutation (D. Sternberg, MD, and S. Vicart, MD, written communication, July 31, 2009).

## COMMENT

Paramyotonia congenita is a dominantly inherited neuromuscular disorder caused by mutations in the *SCN4A* gene that encodes the  $\alpha$  subunit of the skeletal muscle voltage-gated sodium channel. These mutations result in altered skeletal muscle membrane excitability. Nav1.4 is expressed in all skeletal muscles, including those in the larynx. Typically, PMC presents in the first decade of life with cold- and exercise-induced episodic muscle stiffness (myotonia) and muscle weakness, predominantly affecting the muscles of the face and upper limbs.

Hyperkalemic periodic paralysis is a dominantly inherited disorder that is allelic to PMC and is character-

ized by episodes of muscle weakness and myotonia, although weakness is the predominant symptom. In both hyperkalemic periodic paralysis and PMC, 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.<sup>4</sup>

Stridor has been described in both neonates and adults with myotonic dystrophy.<sup>5,6</sup> In addition, there are several reports of stridor in American Quarter Horses affected by the equine form of hyperkalemic periodic paralysis. In one series, 63 of 68 affected horses had stridor in association with exertion, muscle weakness, or excitement.<sup>7</sup> There is also a case report of an adult with PMC in whom provocative testing with muscle cooling induced severe laryngeal myotonia with stridor.<sup>8</sup>

We suggest that it is likely the stridor reflects myotonia of the laryngeal muscles. In addition, the child described here experienced feeding and respiratory difficulties; these were also noted in our previously reported cases of hypotonia,<sup>1</sup> suggesting that 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 Ile693Thr.<sup>1</sup> Taken together, these observations indicate that offspring of parents with sodium channel mutations are at risk for neonatal complications. While 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 described complications so they can counsel mothers and avoid unnecessary investigations of affected neonates.

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