Mutations in SCN4A: A Rare but Treatable Cause of Recurrent Life-Threatening Laryngospasm

abstract

Laryngospasm is a rare but potentially life-threatening occurrence in infants and usually has infective, allergic, metabolic, or anatomic causes. Underlying genetic conditions are rarely considered. Mutations in SCN4A encoding the voltage-gated sodium channel NaV1.4 have been implicated in a wide spectrum of neuromuscular disorders with variable onset, ranging from a rare form of congenital myasthenic syndrome to both hypokalemic and hyperkalemic forms of periodic paralysis and paramyotonia congenita. Here we report on 3 unrelated patients without family history presenting with recurrent, life-threatening episodes of laryngospasm from the first months of life. Clinical features more typically associated with SCN4A-related disorders such as generalized muscle hypertrophy with clinical or electrical myotonia evolved later in life. All patients were found to be heterozygous for the same SCN4A mutation, c.3917G>A; p.Gly1306Glu. Treatment with carbamazepine resulted in complete abolition of recurrent laryngospasm and alleviated symptoms associated with myotonia and muscle stiffness. We conclude that SCN4A mutations ought to be considered in the differential diagnosis of recurrent infantile laryngospasm because timely institution of treatment can be lifesaving. Pediatrics 2014;134:e1447–e1450
Laryngospasm is an acute closure of the glottis caused by sustained laryngeal muscle contractions that may result in stridor, severe respiratory distress, and hypoxia. Acute laryngospasm in children can be caused by intubation, allergic reactions, or even exercise, whereas recurrent episodes may reflect a wide range of underlying medical conditions including electrolyte disturbances (hypomagnesemia, hypocalcemia) and gastroesophageal reflux. Although primary neurologic and neuromuscular causes of recurrent laryngospasm and stridor are rare, they are important to recognize because they are potentially amenable to treatment. Neurologic disorders causing recurrent episodes of laryngospasm and stridor include hyperekplexia, a pronounced startle response to tactile or acoustic stimuli, and seizures, reflecting paroxysmal muscle contractions, whereas certain forms of congenital myasthenic syndromes may present with recurrent stridor or apnea, reflecting fatigable weakness of the laryngeal musculature.

Mutations in SCN4A encoding the voltage-gated sodium channel NaV1.4 cause a spectrum of conditions with overlapping features, including hypokalemic and hyperkalemic periodic paralysis, potassium-aggravated myotonia (PAM), and paramyotonia congenita (PMC). Recent reports suggest that SCN4A-related disorders may present acutely in the neonatal period or early infancy, before evolution of more typical features such as muscle hypertrophy and myotonia.

Here we report on 3 unrelated infants presenting with recurrent episodes of life-threatening laryngospasm, caused by the same heterozygous SCN4A mutation and amenable to carbamazepine treatment.

**PATIENT PRESENTATIONS**

Patient 1 is a 2.5-year-old girl who presented from 8 weeks of age with recurrent acute life-threatening events (ALTEs) that resulted in 4 admissions to the PICU. Typical ALTE episodes were triggered by discomfort and crying (eg, when opening bowels or passing wind), followed by marked stiffness with stridor and increasing distress and eventual apnea and bradycardia. She had been born by normal delivery at 32 weeks' gestation and needed special care infant unit support for 4 weeks. Baseline laboratory investigations; brain imaging; ear, nose, and throat; respiratory, cardiac; and gastroenterology assessments were normal. She continued to make good developmental progress. At 4 months of age a well-defined musculature was noted, prompting an electromyogram that showed myotonic discharges. She was subsequently found to carry a de novo SCN4A mutation (c.3917G>A; p.Gly1306Glu).

Commencement of carbamazepine ≤20 mg/kg per day at 4 months of age instantly and completely abolished ALTEs and resulted in marked improvement of her stiffening episodes. She continues to make good developmental progress. She continues to have eye closure myotonia (ie, difficulty in eye opening after forced eyelid closure).

Patient 2 is a 17-year-old girl who presented from 6 weeks of age with recurrent episodes of laryngospasm associated with stiffness, choking, cyanosis, and occasional loss of consciousness. She had been born at term after a normal pregnancy and needed some oxygen but no resuscitation after birth. Baseline investigations were normal. More specialist investigations (including direct laryngoscopy) performed under the guidance of an ear, nose, and throat surgeon did not reveal evidence of laryngomalacia or other structural abnormalities of the larynx or vocal cords.

She made good motor developmental progress but had mild learning difficulties. From 10 months of age a hypertrophic muscle bulk was noted and became more prominent over time. Episodes of recurrent laryngospasm became increasingly frequent and at some point were considered to be breath-holding spells. Later in childhood she reported that those episodes could be triggered by cold and fizzy drinks, were usually brief, and never resulted in choking or aspiration. From early on, there was also associated episodic stiffness, becoming more prominent over time and on 2 occasions followed by profound nocturnal weakness for several hours. She also suffered frequent muscle spasms, affecting mainly her limbs and the abdominal musculature. Occasional “starey eyes,” caused by involuntary lid retraction, and eye closure myotonia were noted. She rarely experienced intermittent slurring of speech, reflecting tongue involvement. She could sprint but was not able to run long distances, and she did not report a warmup phenomenon. All of her symptoms were more pronounced during the winter.

On examination at 15 years she had a short stature with kyphotic posture and a mild thoracic scoliosis. There was generalized muscle hypertrophy, pronounced around the shoulders and the neck. There was eye closure and hand grip myotonia, both paradoxical for the first 3 or 4 tries. There was percussion myotonia in the hands.

Neurophysiology assessment at 15 years showed profuse myotonic discharges without obvious myopathic features. Short exercise and cooling tests (with rewarming) were within normal limits. There were no sensory or motor nerve abnormalities. In balance, findings were considered consistent with a sodium channel myotonia or PAM.

Sequencing of the HPSG gene prompted by suspicion of Schwartz–Jampel syndrome was normal. Additional genetic testing revealed a heterozygous SCN4A missense mutation (c.3917G>A;...
p.Gly1306Glu). Although initially no positive family history was reported, her 48-year-old father has recently complained of muscle fatigue and delayed relaxation and is currently under investigation.

She was started on carbamazepine at 20 mg/kg per day at 6 years of age under the suspicion of a channelopathy, resulting in remission of laryngospasm and almost complete control of her muscle stiffness. Later in life, she showed intermittent worsening of myotonic symptoms during growth spurts but stabilized again as soon as the carbamazepine dosage was adjusted according to her increased body weight.

Patient 3 is a 6-year-old girl who after a normal perinatal history developed stridor and feeding difficulties from 10 days of age. She was referred from abroad, and review of her case notes suggested that laryngospasm with stridor was intermittent, prompted by similar triggers as noted in the other cases reported in this series, and resulted in repeated hospital admissions earlier in life for “breathing difficulties.” Choking with feeds remained a persistent feature for the first 3 years, but there were no reported apneic spells. Cognition, speech, and motor development were all normal. She has difficulty with physical exercise and tires quickly when writing.

On a recent examination she had generalized muscle hypertrophy, especially in the upper limbs, leading to a “Hulk-like” appearance and a “Hulk-like” stance. There was grip but no eye closure myotonia.

Genetic testing revealed heterozygosity for the SCN4A (c.3917G>A; p.Gly1306Glu) mutation, also carried by her father, who also suffers from myotonia. She has been commenced on carbamazepine recently with favorable response, demonstrating marked improvement of her myotonic symptoms.

**DISCUSSION**

Hypotonia and weakness are infantile presentations of neuromuscular disease that are easily recognized by pediatricians, but for others, such as the episodic apnea or the recurrent stridor seen in genetically distinct forms of congenital myasthenic syndromes, the link is often not immediately obvious. Consideration of an underlying neuromuscular disorder in infants presenting with severe respiratory distress caused by upper airway involvement is important, not only for the institution of effective treatments but also for diagnostic clarification, genetic counseling, and risk assessment for future pregnancies and other children.

Isolated or recurrent episodes of laryngospasm or stridor have a wide range of medical causes, but genetic neurologic or neuromuscular conditions are rarely considered in the differential diagnosis. Our findings suggest that SCN4A-related sodium channelopathies may present with life-threatening infantile laryngospasm early and are a rare but important diagnosis, considering the excellent response to pharmacologic treatments.

In skeletal muscle, normal functioning of sodium channels is essential for the generation and propagation of action potentials along the muscle fiber and, ultimately, the triggering of cellular events that result in muscle contraction. SCN4A encodes NaV1.4, a voltage-gated sodium channel prominently expressed at the neuromuscular junction of striated muscles, including laryngeal muscles. Clinically, SCN4A-related disorders include a wide range of phenotypes, mainly hyperkalemic periodic paralysis (HYPP) and hypokalemic periodic paralysis, PAM, and PMC, with both distinct and overlapping features. SCN4A-related disorders usually present from childhood to adolescence with variable degrees of myotonia and periodic or fixed weakness, but early infantile presentations with features of a congenital myasthenic syndrome, hypotonia, stridor, and respiratory distress have been rarely recognized.

Lion-Francois and colleagues5 coined the term severe neonatal episodic laryngospasm (SNEL), based on a consistent presentation observed in 3 infants harboring de novo dominant SCN4A mutations, characterized by recurrent neonatal life-threatening episodic laryngospasm (fatal in 1 of their cases), subsequent evolution of muscle hypertrophy and myotonia, and good responsiveness to mexiletine. Interestingly, 2 of these infants carried the same SCN4A mutation also found in our patients (c.3917G>A; p.Gly1306Glu). Glycine at position 1306 is a highly conserved amino acid residue and localizes to the III–IV cytoplasmic loop, a portion of the NaV1.4 protein thought to be involved in channel inactivation and, if mutated, is associated with muscle fiber hyperexcitability. Idential or different amino acid substitutions at position p.Gly1306 have been reported in other individuals or families with similar phenotypes. Of note, SCN4A mutations identified in 2 other infants presenting with stridor (p.Thr1313Met) and respiratory distress (p.N1297K), respectively, localize in close proximity to p.Gly1306, suggesting consistent genotype–phenotype correlations for SCN4A mutations affecting the III–IV cytoplasmic loop of the NaV1.4 protein.

Identification of impaired sodium channel inactivation suggests sodium channel blockers as the rational treatment for SNEL and related presentations.12 Our patients showed a dramatic response to carbamazepine treatment, resulting in abolition of life-threatening laryngeal spasms and marked improvement of the myotonia and muscle stiffness, corresponding to observations in recently reported cases with a similar genetic background. Similar beneficial effects have been reported in response to...
drugs with a comparable mechanism of action, such as phenytoin and mexiletine. Considering that the SCN4A-associated episodic laryngospasm may be fatal, an early treatment trial with sodium channel blockers ought to be considered in infants with suggestive features once more common causes have been excluded.

Our findings indicate a relationship between SNEL and other SCN4A-related disorders. p.Gly1306 is also commonly mutated in PAM,9,10 and the cold-induced episodic muscle stiffness in Patient 2 and the variable penetrance in the family do indeed suggest some clinical overlap with this condition. Conversely, stridor has been reported as a clinical feature in humans14 with SCN4A-related PMC and horses with SCN4A-related HYPP.15 The nocturnal paralytic episodes observed in Patient 2 also suggest some clinical overlap with the SCN4A-related HYPP spectrum. Patient 2 also showed some dysmorphic facial features and psychomotor delay similar to those of the patient reported by Gay et al,11 contributing to the initial suspicion of Schwartz–Jampell syndrome.

CONCLUSIONS

Our findings emphasize the importance of recognizing a sodium channelopathy as a potentially treatable cause of severe episodic laryngospasm in neonates and infants. An early treatment trial with sodium channel blockers ought to be considered, after discussion with a pediatric neurologist. In the absence of a positive family history, the diagnosis requires a high degree of suspicion, particularly early in life when more suggestive features are still absent. In families with an established diagnosis of a SCN4A-related disorder, awareness of familial variability will help anticipate neonatal manifestations in affected children that may warrant active management. Sporadic cases may be caused by de novo dominant heterozygous mutations, with potential implications for future offspring.

REFERENCES

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