Diagnosis and Outcome of SCN4A-Related Severe Neonatal Episodic Laryngospasm (SNEL): 2 New Cases

abstract

Mutations of SCN4A encoding the skeletal muscle sodium channel Nav 1.4 cause several types of disease, including sodium channel myotonia. The latter may be responsible for neonatal symptoms, including severe neonatal episodic laryngospasm (SNEL). Establishing the diagnosis of SCN4A-related SNEL early in the neonatal period is crucial because treatment is available that can reduce laryngospasm and improve vital and cerebral outcome. We report 2 new unrelated French patients who presented with SNEL. The first patient was initially diagnosed with laryngomalacia and underwent laryngeal surgery in the neonatal period before being diagnosed with myotonia at 14 months of age. The episodes of laryngospasm disappeared spontaneously, although occasional circumstances such as cold exposure could trigger laryngeal reactions; in addition, he developed myotonia corresponding to an adult myotonia permanens phenotype. This patient is now 24 years old and leading a normal life. The second patient was initially diagnosed with gastroesophageal reflux, then SNEL; his condition improved with carbamazepine treatment, and he is now 6 months old. The diagnostic sequence in both patients was the same: first, severe episodic apneic attacks necessitating hospitalization occurring in the first week of life; second, observation of muscle hypertrophy and peripheral hypertonia with a clear myotonic pattern on electromyogram (at 14 and 3 months of age, respectively); third, genetic testing revealing de novo SCN4A G1306E mutation. Both patients have had good therapeutic response to sodium channel blockers (carbamazepine or mexiletine). Pediatrics 2013;132:e784–e787

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neonate, laryngospasm, myotonia, SCN4A

ABBREVIATION
SNEL—severe neonatal episodic laryngospasm

Dr Caietta conceptualized and designed the study and drafted the initial manuscript; Drs Milh, Lépine, and McGonigal reviewed and revised the manuscript; Dr Sternberg performed the molecular genetic studies and critically reviewed the manuscript; Dr Boulay performed the electromyogram and designed the figure and video; Pr Chabrol coordinated and supervised the manuscript and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Skeletal muscle channelopathies usually present as childhood onset dominant disorders, in the form of periodic paralysis, paramyotonia congenita, or sodium channel myotonia.\textsuperscript{1–4} It has been shown recently that these can manifest as neonatal disorders, either hypotonia or stridor\textsuperscript{6,6} or potentially severe episodic apnea.\textsuperscript{7,8} In particular, de novo mutations may be responsible for severe cases with no family history.\textsuperscript{7,8} Therapeutic agents, such as sodium channel blockers, are available for those disorders and can help in treating neonatal manifestations. It is therefore important to recognize SCN4A-related neonatal disorders promptly and treat them appropriately. Unfortunately their rarity means that misdiagnosis and inappropriate treatment may occur, eventually contributing to poorer outcome. One of these SCN4A-related disorders manifests as severe neonatal episodic laryngospasm (SNEL). Laryngospasm is involuntary muscular contraction of the laryngeal cords, causing partial obstruction during inspiration. In children, the condition can be lethal, leading to cardiac arrest within 30 to 45 seconds, and is a possible cause of death or cerebral hypoxia. In neonates laryngospasm occurs mainly after tracheal extubation or during intubation but can also result from hypocalcemia, gastroesophageal reflux, epileptic seizure, congenital myasthenic syndrome, or myotonia. We report 2 previously unpublished cases, unrelated French patients with de novo SCN4A mutations presenting with severe neonatal episodic laryngospasm; 1 patient is now 24 years old, with a favorable outcome.

**CASE REPORTS**

**Patient 1**

Patient 1 was the second child of non-consanguinous parents, born in 1988. There was no family history of note. Pregnancy and delivery were unremarkable, with birth weight of 3.9 kg and an Apgar score of 10/10. Shortly after birth, episodic apneas appeared, necessitating hospitalization in NICU. A diagnosis of laryngomalacia was made, and the baby was discharged with medical treatment of gastroesophageal reflux. Frequent episodes of stridor and apnea persisted, associated with cyanosis. Laryngomalacia surgery was performed but did not improve the symptoms. At 14 months, he was hospitalized during the winter because of a severe episode of cyanosis and apnea provoked by exposure to cold. On examination, muscle hypertrophy was noted, especially of sternocleidomastoids. He had an athletic appearance, and limb movements were limited by hypertrophy. Electromyography revealed marked myotonia, and muscle biopsy showed enlarged fibers without dystrophy. A diagnosis of myotonia congenita was postulated and treated with mexiletine initiated, leading to partial improvement of muscle stiffness. However, during early childhood (2–8 years of age), episodes of diplopia, strabismus, and dysphagia for cold drinks appeared. At 8 years of age (1996), he presented with an episode of sweating and tachycardia apparently induced by cold temperatures. He experienced generalized muscular contractions, predominantly in the legs, lasting from several hours to a whole day, which were present on awakening and improved with effort (warmup phenomenon). Clinical examination revealed normal strength but significant generalized muscle hypertrophy. He was treated with acetazolamide combined with mexiletine, with good symptomatic relief. At 15 years of age (2003), sequencing of the SCN4A gene showed a heterozygous de novo G1306E mutation in exon 22. He is now 24 years old, having completed high school and obtaining a diploma in computer science. He still experiences generalized cramps worsened by cold, exercise, and tiredness but has no limitation of walking distance, even on stony ground, and can run. Clinical examination shows myotonia detectable from first muscular contraction and trapezium and paravertebral muscle contracture but no muscle weakness.

**Patient 2**

The patient is the first child of non-consanguinous parents, born in March 2012. Oligohydramnios and intrauterine growth retardation were noted during the seventh month of pregnancy. Measurements at birth after 39 weeks' gestation were 2,920 kg for weight, 48 cm for height, and 34 cm for head circumference, with an Apgar score of 10/10. His parents noticed breathing difficulty from birth, and during the first week of life he presented with daily episodes of apnea; he was therefore hospitalized at 1 month of life. At this time gastroesophageal reflux was diagnosed and treated, and he went home after 2 weeks. However, frequent daily episodic dyspnea persisted, sometimes occurring more than once per hour, leading to admission to the ICU at age 3 months. In the ICU it was noted that the apneic episodes were associated with initial stridor followed by generalized stiffness, facial contraction, cyanosis, and bradycardia, generally without loss of consciousness; these episodes lasted a few seconds, with rapid recovery. Between attacks, neurologic examination showed slight peripheral hypertonia with hypertrophy of limb muscles and clenched hands; spontaneous movements were poor, without muscle weakness, and physiologic tendon reflexes were present. Psychomotor development was normal. Investigations including electroencephalography, brain imaging, and serum potassium levels were normal. Electromyography revealed permanent...
spontaneous muscle activity with myotonic discharges (Supplemental Video 1 and Fig 1) and allowed the diagnosis of myotonic SNEL. Rapid sequencing of the \textit{SCN4A} gene showed a heterozygous c.3917G$\rightarrow$A mutation predicting a p.Gly1306Glu missense, which has previously been associated with SNEL.\textsuperscript{8} Genetic analysis of parents confirmed that the mutation was de novo. Treatment with carbamazepine was initiated at 3.5 months, titrated up to 12 mg/kg/day. Laryngospasms diminished in frequency and intensity within 1 week, allowing discharge from hospital. One month after the beginning of treatment, only 2 or 3 daily episodes of dyspnea occurred. Clinical examination revealed persistent global hypertonia and hypertrophic muscles but better use of the hands.

**DISCUSSION**

We report 2 new cases of G1306E de novo mutation in \textit{SCN4A} presenting with episodic laryngospasm during the first days of life. SNEL as the initial presentation of sodium muscle channelopathy has already been reported.\textsuperscript{6–8} Correct diagnosis is crucial given the possibility of fatal outcome, although the G1306E mutation seems to have better prognosis than N1297K\textsuperscript{7} or A799S.\textsuperscript{8} The condition may be easily mistaken for laryngomalacia or gastroesophageal reflux, as was the case in our patients; such misdiagnosis could clearly be deleterious, eventually leading to unnecessary surgery or repeated hospitalization in the neonatal period. Thus in the presence of laryngospasm, clinical examination must be rigorous and peripheral hypertonia and hypertrophy of muscles should be sought. Altered muscle anatomy most often appears secondarily, and diagnosis is difficult during the first months of life.\textsuperscript{8} Family history (muscle stiffness, cold- and exercise-induced phenomena, or similar episodes in family members suggesting dominant inheritance) may offer important clues allowing earlier diagnosis, but in our 2 patients, mutations were de novo. In patient 1, the laryngospasm gradually disappeared in the second year of life. In patient 2, carbamazepine treatment produced rapid improvement. Although the case of patient 1 shows that SNEL may spontaneously disappear in the first years of life, treatment by sodium channel blockers is nevertheless appropriate because this avoids severe life-threatening events and improves myotonic symptoms. In France, 4 cases of neonatal laryngospasm caused by G1306E de novo mutation have been diagnosed over the last 5 years, which suggests that this disorder may be more common than previously thought and probably is underdiagnosed in infancy. The two other reported cases were effectively treated with carbamazepine in one case and mexiletine in the other.\textsuperscript{8}

Glycine on site 1306 is important for sodium channel inactivation in the \(\alpha\)-subunit.\textsuperscript{9} The substitution of glutamic acid for glycine is located between repeat III and IV in exon 22 and is responsible for slower sodium fast channel inactivation and an increase in late channel opening, resulting in durable muscle depolarization and muscle fiber hyperexcitability. This G1306E substitution is associated with the most intense form of sodium channel myotonia, myotonia permanens.\textsuperscript{10} Cold sensitivity may be observed in this condition, and respiratory involvement is possible although not common.\textsuperscript{10} Other substitutions at this codon (glycine to valine, glycine to alanine) have milder biophysical effects and are associated with a milder form of sodium channel myotonia, myotonia fluctuans,\textsuperscript{11} in which no neonatal symptoms have been reported.

**FIGURE 1**

Patient 2 (3 months), insertional and spontaneous activity: single fiber discharge from the tibialis anterior. The tracings showed a train of positive sharp waves.
Electromyography is a sensitive and specific tool permitting diagnosis of electrical myotonia in patients with episodes of stiffness. It shows a unique pattern in children and adults with SCN4A G1306E-related myotonia permanens characterized by abundant large-amplitude rhythmic discharges that are spontaneous, permanent, and ubiquitous. This myotonic activity is triggered by insertion of the fine needle electrode but also by external sources of excitation. Myotonic discharges are high-amplitude positive sharp waves and constitute complex repetitive discharges (Fig 1). This pattern was observed in our two patients at 3 and 14 months of age, thus showing that permanent myotonic activity is present soon after birth in SCN4A G1306E carriers. This electromyographic pattern is characteristic of SCN4A-related SNEL in neonates with episodic laryngospasm.

In summary, severe laryngospasm in the neonate may result from G1306E-related myotonia permanens or other SCN4A-related myotonias. For the clinician evaluating neonatal laryngospasm, rigorous clinical analysis is needed in order not to miss this diagnosis, and hypertrophy of muscle and peripheral hypertonia must be looked for. Electromyography may show a specific spontaneous, permanent, and ubiquitous myotonic pattern. Family history is often negative because mutations are de novo in most cases; detection of mutation in SCN4A confirms the diagnosis. Treatment by sodium channel blockers helps reduce morbidity and mortality; the natural history is one of spontaneous improvement of laryngeal symptoms in childhood and adulthood, the peripheral myotonic impairment being compatible with a normal life.

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