Severe neonatal episodic laryngospasm (SNEL) due to a mutation in the skeletal muscle voltage-gate sodium channel: a case report and review of the literature.

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ABSTRACT

The occurrence of episodic stridor and respiratory arrest during the neonatal period has been known since 2008 as a critical and life-threatening presentation of skeletal muscle voltage-gate sodium channelopathy. Notwithstanding this syndrome has been formally defined only in 2010, when the acronym SNEL has been coined. Up to date 18 cases has been described in the literature, of those at least 9 were due to a p.G1306E mutation of the *SCN4A* gene.

Myotonia is rare in neonatal period, usually becoming manifest only in late childhood or adolescence, but its prompt recognition, in particular when the respiratory function is involved, is of critical importance to provide a potentially life-saving treatment.

Here we present the 28-year-long history of a patient who presented dramatic episodes of laryngospasm and cyanosis in very early life and then developed a severe non-dystrophic myotonia. Genetic tests detected a G1306E mutation in the *SCN4A* gene, which is the most frequent mutation associated to SNEL. Treatment with mexiletine since early infancy abolished the respiratory paroxysms and significantly reduced myotonia over years, permitting a satisfactory quality of life.

Documenting a new case of SNEL, we aim to stress the significance of early diagnosis of this potentially life-threatening but treatable syndrome, and to illustrate the phenotypical variability and the natural history over a 28-year-long follow-up.

CASE REPORT

We present the case of a 28-year-old male, who presented at the age of 20 days repeated paroxysmal episodes of diffuse hypertonia associated with stridor, respiratory distress and cyanosis. Since the age of 45 days, his appearance was featured by a diffuse muscle hypertrophy and umbilical and inguinal hernias. During early childhood clinical myotonia became manifest at distal arms, eyelids and masticatory muscles, resulting in deformation of the hands; any overt modification with temperature, exercise or alimentation wasn't apparent. Motor development stages were delayed but mental performance were normal. Physical and neurological examination disclosed constant diffuse hypertrophy of skeletal muscles, more pronounced in the neck and limb girdles, slight hypotonia, deformation of hands and lumbar hyperlordosis. Clinical myotonia was evident at the hands, feet and eye-lids, after voluntary contraction or muscle percussion, but "warm-up effect" wasn't detected. Since he was 19 years old, he experienced transitory flaccid weakness in the limbs and neck; concomitant measurement of hematic potassium wasn't performed. Any persistent reduction in muscular strength wasn't observed. EMGs constantly showed abundant diffuse myotonic discharges. Seric CK levels were up to 10 times over the normal values. Cardiological check-ups ruled out any apparent anatomical, mechanical or electrophysiological alteration. The first hypothetical diagnosis was of myotonia congenita (Thomsen disease), but genetic tests showed non-pathological polymorphisms in the *CLCN1* gene and a p.G1603E mutation in the *SCN4A* gene, known to be associated with *miotonia permanens* and SNEL. The samples from the parents were negative, suggesting a *de novo* mutation.

The patient was treated with mexiletine 30 mg qid, during infancy, up to 400 mg tid, andacetazolamide 125 mg + 125 mg + 62,5 mg per day. The myotonic phenomenon was markedly attenuated by pharmacological treatment. Association of carbamazepine 100 mg per day was ineffective. Moreover, a low potassium diet was tried, but did not produce any overt effect. Optimization of the pharmacological therapy also led to the apparent resolution of the episodes of weakness.

At present the patient has graduated and is employed in a national scientific research institution, experiencing only minimal disability.

Reference	Age of onset	*SCN4A* mutation	Respiratory symptoms	Myotonia	Muscle hyper--trophy	Muscle tone	Episodic weakness	Treatment	Outcome
Gay et al. 2008	At birth	N1297K	Apneas and hypoxia	+	+	↑	Cold-induced	Mexiletine	Fatal pneumonia at 20 months
Matthews et al. 2008	At birth (2/6) On day 1 (4/6)	I693T	Oxygen desaturation (2/6)	n.r.	n.r.	↓ (6/6)	n.r.	No specific treatment	Good (6/6)
Lion-Francois et al. 2010	On day 16 (1/3) At birth (1/3) On day 3 (1/3)	G1306E (2/3) A799S (1/3)	Laryngospasm	3/3	3/3	↑ (1/3)	n.r.	Mexiletine (1/3) CBZ (1/3)	Good (2/3) Fatal respiratory arrest (1/3)
Matthews et al. 2011	On day 1	T1313M	Laryngospasm	+	n.r.	n.r.	Cold-induced	Mexiletine	Good
Desaphy et al. 2012	At birth	G1603E	n.r.	+	+	+	n.r.	Flecainde	Good
Caietta et al. 2013	At birth (2/2)	G1603E	Laryngospasm (2/2)	2/2	2/2	↑ (1/2)	n.r.	Mexiletine + acetazolamide (1/2) CBZ (1/2)	Good (2/2)
Singh et al. 2014	At 8 weeks (1/3) At 6 weeks (1/3) On day 10 (1/3)	G1603E	Laryngospasm (3/3)	3/3	2/3	n.r.	1/3	CBZ (3/3)	Good (3/3)
Portaro et al. 2016	At birth	G1603E	Laryngospasm	+	+	↑	n.r.	Flecainide	Good
Present case	On day 20	G1603E	Laryngospasm	+	+	↑	+	Mexiletine + acetazolamide	Good

CONCLUSIONS

SNEL is a recently described and rare neonatal-onset syndrome in patients affected by skeletal muscle voltage-gate sodium channelopathy. It is still debated if SNEL should be considered as a distinct syndrome or just a particular presentation of *miotonia permanens*, inasmuch they share common genetic substrate and similar clinical pictures beyond infancy. With regard to this, we point out the atypical aspects of the myotonic phenomenon and the recurrent episodes of weakness in our case and others; these elements hardly fit in a proper diagnosis of *miotonia permanens*, corroborating the view of SNEL as an autonomous clinical entity in the spectrum of skeletal muscle sodium channelopathies. It's also noteworthy that the improvement in myotonia control with specific pharmacotherapy abated the adynamic phenomena.

A correct and prompt diagnosis of SNEL has extremely relevant prognostic implication because the specific therapy with mexiletine or flecainide could be life-saving and could prevent persistent hypoxic damages to the CNS. Even though this treatment is generally well tolerated, it should be stressed that a life-long treatment with such anti-arrythmic drugs mandates a careful and regular cardiological monitoring, even more prudent when the patient is a newborn or a child. Furthermore such a treatment should be repeatedly adapted to the evolving natural history of the disease and patient's subjective needs and demands over years.

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