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Case report

De novo variant in *SCN4A* causes neonatal sodium channel myotonia with general muscle stiffness and respiratory failure

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Abstract

Variants of the skeletal muscle sodium channel gene *SCN4A* are associated with different neuromuscular disorders including sodium channel myotonia. Here, we report an infant with a *de novo* variant in *SCN4A* presenting with neonatal onset of severe muscle stiffness with involvement of facial and eyelid muscles, and life-threatening events with respiratory failure due to severe apnoea and thorax rigidity. The boy dramatically improved in both respiratory and motor function under carbamazepine therapy.

Keywords: *SCN4A*; Myotonia; Respiratory failure; Muscle stiffness.

1. Introduction

Non-dystrophic myotonias are a rare group of neuromuscular disorders caused by variants in skeletal muscle sodium (*SCN4A*) or chloride (*CLCN1*) channel genes. Variants in *SCN4A* are associated with different phenotypes such as paramyotonia congenita, hyper- or hypokalemic periodic paralysis, sodium channel myotonia but also with congenital myasthenic syndromes and congenital myopathies [1,2]. Clinical symptoms are mainly characterized by episodes with muscle stiffness or paralysis triggered by exercise, cold, infections or fasting [2,3]. Infantile onset of myotonia is very rare. There are single cases described of a *SCN4A* associated sodium channel myotonia with infantile onset of muscle stiffness and respiratory failure due to laryngospasm [4–6]. Here, we report an infant with a *de novo* variant in *SCN4A* presenting with neonatal onset of severe muscle stiffness, and life-threatening events with respiratory failure due to severe apnoea and thorax rigidity.

2. Case report

The boy was delivered by a 30-year-old mother at 33 weeks of gestation by Caesarean section due to premature labor and amniorrhexis. APGAR scores were 1/2/6. During the last days of pregnancy, reduced child movements were reported and a clubfoot was diagnosed on ultrasound. The boy developed respiratory failure immediately after birth and required non-invasive ventilator support due to an insufficient spontaneous breathing pattern and recurrent apnoea. He presented with a general increased muscle tonus and stiffness with involvement of facial and lid muscles, bilateral hip luxation, and left-sided club foot (Fig. 1). There were no facial dysmorphism or muscle hypertrophy. Due to the muscle stiffness and thorax rigidity, bag-valve-mask

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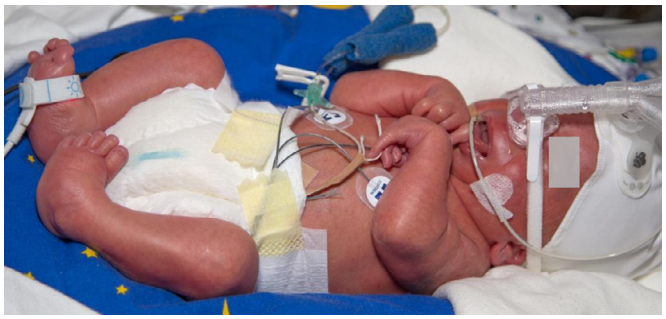

Fig. 1. Postnatal clinical presentation with general muscle stiffness, bilateral hip luxation, left-sided club foot, and the need of non-invasive ventilation.

ventilation was not effective during episodes, and invasive ventilation, including high frequency oscillation ventilation, with analgosedation and muscle relaxation became necessary from the age of 19 days. No episodes with stridor or laryngospasm were reported.

Cardiac, cerebral and metabolic tests showed normal results. Laboratory testing revealed hyperCKaemia (2930 U/l (normal 2–163 U/l) within the first weeks of life. EMG of the *M. vastus lateralis* showed continuous myotonic discharges (Fig. 2). Genetic testing revealed a heterozygous *de novo* variant c.2386C>G (p.Leu196Val) in *SCN4A* and a heterozygous c.409T>G (p.Tyr137Asp) variant in *CLCN1*. Both variants are either absent (*SCN4A*) or very rare (*CLCN1*, 3 heterozygous, no homozygous carriers) in gnomAD and predicted damaging. The *SCN4A* variant was not detectable in both parents. The parents did not agree to a segregation study for the *CLCN1* variant.

At the age of 5 weeks, we started treatment with carbamazepine (initial dose of 10 mg/kg/day) and observed an improvement in respiratory function so that invasive ventilation could be weaned after another 6 days. The boy was discharged from hospital at the age of 2 months without any ventilator support. Under treatment with carbamazepine (36 mg/kg/day), there were no further life-threatening events with apnoea or thorax rigidity. Creatine kinase decreased to values in the normal range. Up to the most recent examination at the age of 18 months, the boy continuously improved in motor function: he gained the ability to sit unassisted and started to raise and stand with assistance. He still showed variable ptosis on both sides. He received a brace treatment according to the PONSETI method for his clubfoot and a closed reduction of hip luxation was performed at the age of 18 months.

3. Discussion

The clinical phenotype of *SCN4A* variants is very heterogeneous and infantile onset of symptoms is rare with only single cases of myotonia and general muscle stiffness reported. In patients with a c.3917G>A variant in *SCN4A*, recurrent episodes with paroxysmal muscle stiffness, stridor and laryngospasm were described [4–6]. Lion-Francois et al. reported of a patient with a c.2395G>T variant in *SCN4A* with respiratory distress at birth and generalized hypertonia, including facial and lid muscles [4]. Additionally, in a cohort of infants with sudden infant death syndrome (SIDS), four children with functionally disruptive *SCN4A* variants leading to respiratory and laryngeal failure were identified [7]. Fusco et al. described a girl with neonatal onset of diffuse stiffness predominant in lower limb and abdomen, bilateral clubfoot deformity, hip dislocation and lower limb areflexia, without respiratory failure caused by a c.3539A>T variant in *SCN4A* [8].

We here report a *de novo* c.2386C>G variant in *SCN4A* that has not been described before. The phenotype was characterized by neonatal onset of general muscle stiffness, severe respiratory failure due to apnoea and thorax rigidity, clubfoot deformity and hip luxation. *SCN4A* encodes the alpha subunit of the skeletal muscle voltage-gated sodium channel NaV1.4 so that variants in *SCN4A* affect the gating behavior or ion current passing through Nav1.4 [1]. The additional heterozygous variant in *CLCN1*, which in isolation is not considered pathogenic, might additionally modify the phenotype of our patient.

Treatment with carbamazepine or mexiletine was shown to improve muscle stiffness but also to stabilize respiratory function in infants with *SCN4A* variants [4–6] as they block the open state of Nav1.4. In our patient, drug treatment with carbamazepine led to marked and continuous improvement in respiratory and motor function.

The severe and prolonged muscle stiffness in our patient involved a generalized increased muscle tone resembling

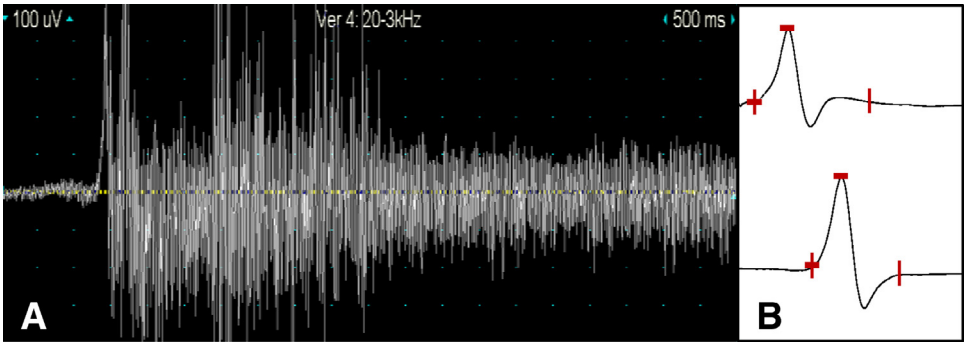

Fig. 2. (A) EMG of the right *M. vastus lateralis* with myotonic discharges. (B) Normal nerve conduction study of the right *N. tibialis*.

myotonia permanens with typical electromyographic findings in the *M. vastus lateralis*, which may explain the initial hyperCKaemia. The ptosis was not fatigable and thus most likely caused by eyelid myotonia that has been reported as typical paediatric manifestation of *SCN4A* myotonia [9]. Both, muscle stiffness and ptosis improved under treatment with carbamazepine. We could not observe an exacerbation of stiffness by different trigger factors such as cold or potassium. In addition to the severe myotonia, our patient showed bilateral hip luxation and left-sided club foot, phenotypically overlapping with congenital myopathy and congenital myasthenic syndromes [10–12]. However, there were no further, clinical signs of muscle weakness, hypotonia or fatigability in our patient as previously described in patients with congenital myasthenic syndromes caused by *SCN4A* variants Our patient did not undergo repetitive nerve stimulation or single-fiber EMG to investigate a potential neuromuscular transmission defect.

In conclusion, the differential diagnosis of a generalized increased muscle tone in infants is difficult, and therefore this treatable condition can be easily missed. Neonatal onset of symptoms in sodium channel myotonia is rare but might cause life-threatening events such as SIDS or severe respiratory failure. However, with the availability of an effective therapy, early diagnosis and treatment of sodium channel myotonia are crucial for these infants.

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