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BRIEF COMMUNICATION

Periodic breathing in patients with *NALCN* mutations

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Abstract

Biallelic mutations in *NALCN* are responsible for infantile hypotonia with psychomotor retardation and characteristic facies 1 (IHPRF1). Common features of this condition include severe neonatal-onset hypotonia and profound global developmental delay. Given the rarity of this condition, long-term natural history studies are limited. Here, we present a 9-year-old male with a homozygous nonsense mutation in *NALCN* (c.3910C>T, p.Arg1304X) leading to profound intellectual disability, seizures, feeding difficulties, and significant periodic breathing. Breathing irregularity was also reported in three previous patients; similar to our patient, those children demonstrated periodic breathing that was characterized by alternating apneic periods with deep, rapid breathing. As the phenotype associated with *NALCN* mutations continues to be delineated, attention should be given to abnormal respiratory patterns, which may be an important distinguishing feature of this condition.

Introduction

Biallelic mutations in *NALCN* are responsible for infantile hypotonia with psychomotor retardation and characteristic facies 1 (IHPRF1, OMIM #615419) [1, 2]. IHPRF1 is an extremely rare condition [1–5]. The common features of this condition include severe neonatal-onset hypotonia and profound global developmental delay. Other features include a lack of speech, severe feeding difficulties, constipation, respiratory abnormalities, and seizures. Given the rarity of this condition, long-term natural history studies are limited. We present a 9-year-old male with a homozygous nonsense mutation in *NALCN* leading to profound intellectual disability, seizures, feeding difficulties, and a unique periodic breathing pattern.

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Clinical report

The proband is the first child of a consanguineous healthy couple of Turkish descent. The pregnancy was complicated by severe oligohydramnios and decreased fetal movements. He was delivered at 33 weeks gestational age. Birth weight was 1848 g (27th centile) and head circumference was 30 cm (10–50th) (Table 1). APGARs were 4 at 1 min and 7 and 5 min. He was intubated at 10 min of life for respiratory distress syndrome. He was weaned off ventilation at 7 days of life. Abdominal ultrasound showed bilateral cryptorchidism and inguinal hernias. Head ultrasound was normal. His neurologic examination was unremarkable and he was discharged home at 3 weeks of life.

At 10 weeks corrected age, he was admitted to hospital for investigation of periodic rapid breathing. Examination at that time revealed a normally grown infant with hypotonia. He was unable to visually fixate or follow objects. He showed dysconjugate eye movements and horizontal nystagmus. Deep tendon reflexes were brisk with pathologic clonus at the ankle. His magnetic resonance imaging (MRI) brain, electromyography, electrocardiogram, echocardiogram, and chest X-ray were unremarkable.

By 1 year of age, profound global developmental delay was apparent. At 16 months, he required a gastrostomy tube for failure to thrive. At 18 months, periodic breathing was again noted, which prompted a sleep study. The breathing pattern was similar in awake and asleep states with three to four rapid deep breaths followed by central apneas (mean

Table 1 Clinical and genetic characteristics of individuals with *NALCN* mutations

Series	Current	Koroglu et al. [1]		Al-Sayed et al. [2]						Gal et al. [3]			Takenouchi et al. [4]		Total
Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Mutation	c.3910C>T, p.Arg1304X	c.1924C>T, p.Gln642Glu		c.1489delT, p.Tyr497Thrfs*21			c.3860G>T, p.Trp1287Leu			p.3390G>A, IVS29-1G>A			c.1267-2A>G	c.2022_23delAT, p.Cys675Leufs*23	
Type	Nonsense	Missense		Frameshift			Missense			Splicing			Splicing	Frameshift	
Age (yr), gender	9 M	21 F	18 M	7 M	7 M	4 M	17 F	16 F	9 F	1.7 M[a]	8 F	5 F[a]	4 F	11 M	
Birth weight	1848 g	2200 g	2350 g	2600 g	4000 g	2500 g	2800 g	3000 g	2800 g	3090 g	3000 g	3200 g	2188 g	2216 g	
	−0.7 SD	−2.3 SD	−2 SD										−1.2 SD	−2.1 SD	
Failure to thrive	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	9/14, 64%
Microcephaly	No	Yes	Yes	No	No	No	N/a	No	No	Yes	Yes	Yes	No	No	5/13, 38%
Severe ID	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14/14, 100%
Speech delay	Yes, none	Yes, none	Yes, none	Yes, none	Yes, none	Yes, none	Yes, delay	Yes, delay	Yes, delay	Yes, none	Yes, none	Yes, none	N/a	N/a	12/12, 100%
Hypotonia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14/14,100%
Vision abnormality	Yes, St, Ny	Yes, St, Ny, Oa	Yes, Ny, Oa	Yes, Eso	Yes, Anis	No	No	No	Yes, St	Yes, St	Yes, St, Ny	Yes, St, Op	Yes, Eso	Yes, Eso	11/14, 79%
Hearing loss	No	SNHL	SNHL	No	No	No	No	No	No	N/a	N/a	N/a	N/a	N/a	2/9, 22%
Seizures	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	No	No	8/14, 57%
Seizure onset	3 yr	13 yr	8 yr				7 yr	7 yr	3 yr		4 yr	4 yr			
Breathing irregularity	Yes	No	No	No	No	No	No	No	No	Yes	Yes	Yes	No	Yes	5/14, 29%
Constipation	Yes	N/a	N/a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12/12, 100%
Cryptorchidism	Yes	—	Yes	Yes	Yes	Yes	—	—	—	N/a	—	—	—	N/a	5/5, 100%

M male, *F* female, *yr* years old, *N/a* not available, *St* strabismus, *Ny* nystagmus, *Oa* optic atrophy (progressive), *Eso* esotropia, *Anis* anisometropia, *Op* ophthalmoplegia, *SNHL* sensorineural hearing loss, *ID* intellectual disability

[a]Deceased

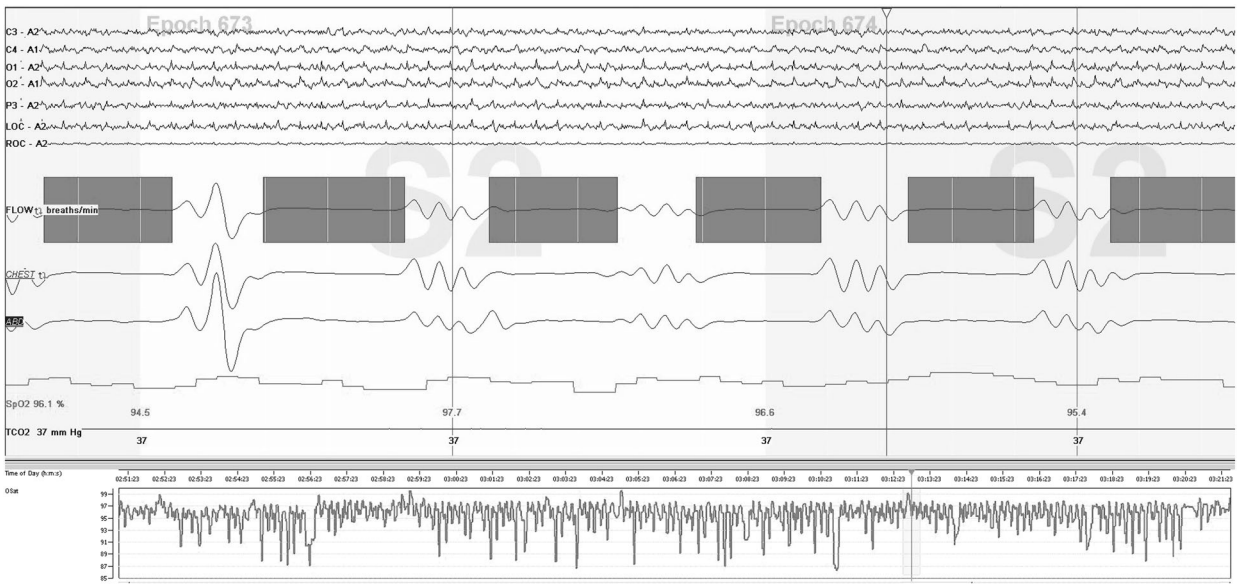

Fig. 1 Figure 1 shows the respiratory pattern present throughout sleep (sleep staging impossible based upon electroencephalogram, done by direct observation). Top box shows two 30 s epochs (total 1 min recording), bottom box shows 30 min of saturation monitoring from 2:50 to 3:20 am. During sleep, he showed persisting pattern of 2–4 breaths followed by a 6–8 s apnea, with desaturations down to 85–90% followed by return to baseline (95–97%). This pattern was present throughout sleep. Transcutaneous CO_2 remained stable throughout at around 37 mmHg

duration of 7.5 s). The longest apneas were 11.6 s and the lowest recorded oxygen saturation was 85.4%. Transcutaneous CO_2 recordings were normal. His central apnea/hypopnea index (AHI) was 320/h (normal <5/h) (Fig. 1). Electroencephalogram (EEG) revealed diffuse slowing but no electrographic seizures. A sleep study at 3 years old showed similar results (AHI 241/h).

At 3 years of age, he developed brief seizures characterized by behavioral arrest, posturing of his limbs, followed by complete loss of tone. He has since developed infrequent generalized tonic–clonic seizures that are well controlled on levetiracetam.

At 9 years of age, he remains non-verbal, unable to sit or ambulate independently, and unable to manipulate objects with his hands. His most recent examination showed a small, non-dysmorphic male (weight 24 kg, 11th centile; head circumference 51.8 cm, 33rd centile) with axial hypotonia and brisk deep tendon reflexes. He continues to demonstrate profound periodic breathing awake and asleep.

Microarray was significant for eight long (>10 Mb) continuous stretches of homozygosity covering 138 Mb. Serum creatine kinase, lactate, and plasma amino acids were normal. Quadriceps muscle biopsy was unrevealing. An intellectual disability panel of 169 genes did not identify a pathogenic or likely pathogenic variant. Repeat MRI brain at 6 years old was unremarkable.

Due to the lack of diagnosis, our patient was enrolled in the Care4Rare Canada research project. Research ethics board approval was obtained, as was free and informed consent. Exome sequencing was performed and analyzed as previously described [6–8]. Average coverage was 125× with 97.8% of Consensus Coding Sequence (CCDS) exons were covered at >10×. All variants in known disease genes present in OMIM and/or Orphanet were assessed. A homozygous nonsense variant in *NALCN* (NM_001350748.1, c.3910C>T, p.Arg1304X) was identified and validated by Sanger sequencing. This variant has never been observed in affected individuals in the literature, HGMD, or ClinVar. It has been observed in the heterozygous state in two presumed healthy controls in gnomAD (Minor Allele Frequency (MAF) = 0.0008). There were no other variants in genes with any relevance to the patient's phenotype.

Discussion

The clinical features that are common to patients with biallelic *NALCN* mutations are severe intellectual deficiency, speech delay, and hypotonia. Most patients do not develop expressive language (Table 1). Constipation and cryptorchidism are also common. Seizures are present in just over half of patients with a mean age of onset of 6.1 years old. Visual abnormalities have been reported in 79% patients.

Breathing irregularity was a prominent feature in our patient and three previous patients [3]. Similar to our patient, these children demonstrated apneas or periodic breathing that was characterized by alternating apneic periods with deep, rapid breathing.

Lu et al. [9] described that mice with homozygous knockout of *Nalcn* die within the first day of life secondary to severe disruption in their respiratory rhythm with alternating apneas punctuated by short episodes of deep breathing. They demonstrated that *Nalcn*-deficient mice lacked the rhythmic electrical discharges required for normal respiration and postulated that this abnormal breathing pattern was likely due to abnormal central control of the diaphragm. Our patient's sleep study revealed a highly irregular breathing pattern and frequent central apneas with oxygen desaturation, consistent with a severe disturbance in the central control of respiration. We propose that the homozygous nonsense mutation in *NALCN* in our patient could mimic the knockout phenotype seen in the mouse model.

The *NALCN* gene encodes a non-selective sodium leak channel that is expressed mainly in the central nervous system [1, 9] and plays a role in nerve-resting conductance and excitability [9, 10]. Dominant, gain-of-function mutations in *NALCN* are responsible for a different clinical entity: congenital contractures of the limbs and face with hypotonia and global developmental delay (CLIFAHDD syndrome, OMIM #616266) [11–13]. The respiratory phenotype has not been reported with CLIFAHDD. This variability in phenotype may suggest that NALCN has multiple roles and mechanisms of action in the central nervous system. NALCN is part of a larger protein complex which includes UNC-80 and UNC-79, among others [10]. The presence of all proteins is required for proper channel function [14]. Biallelic mutations in *UNC80* cause IHPRF2 [15, 16]; however, no respiratory phenotype has been reported with that condition.

The differential for alternating apneic and hyperventilation episodes includes Pitt–Hopkins syndrome, Rett syndrome and variants, Joubert syndrome, and metabolic conditions such as fructose-1,6-bisphosphatase deficiency. As the phenotype associated with *NALCN* mutations continues to be delineated, attention should be given to abnormal respiratory patterns, which may be an important distinguishing feature of this condition.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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