Clinical commentary

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Neonatal tremor episodes and hyperekplexia-like presentation at onset in a child with *SCN8A* developmental and epileptic encephalopathy

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ABSTRACT – *SCN8A* encephalopathy is a newly defined epileptic encephalopathy caused by *de novo* mutations of the *SCN8A* gene. We report herein a four-year-old boy presenting with severe non-epileptic abnormal movements, of possibly antenatal onset, progressively associated with pharmacoresistant epilepsy and regression, associated with a *de novo* heterozygous missense mutation of *SCN8A*. This case shows that paroxysmal non-epileptic episodes of severe tremor and hyperekplexia-like startles and a striking vegetative component can be the first early symptoms of severe *SCN8A* developmental and epileptic encephalopathy. Clinicians should be aware of these symptoms in order to avoid misdiagnosis and ensure early appropriate therapeutic management. [*Published with video sequences on www.epilepticdisorders.com*].

Key words: *SCN8A*, developmental and epileptic encephalopathy, hyperekplexia-like, tremor, movement disorder

VIDEOS ONLINE

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The term "developmental and epileptic encephalopathy" (DEE) refers to a newly defined group of conditions characterised by the co-occurrence of epilepsy and developmental delay, beginning in the neonatal period or in infancy, typically with developmental plateauing or regression associated with frequent epileptiform activity and pharmacoresistance (Scheffer *et al*., 2017). Various phenotypes with abnormal non-epileptic movements may occur. Over recent years, next-generation sequencing (NGS) technology has proved to be a powerful tool to identify novel disease-causing genes for epileptic encephalopathies (Epi4K Consortium *et al*., 2013).

SCN8A encephalopathy is a type of DEE caused by *de novo* mutations in the gene that encodes the neuronal sodium channel voltage-gated α8-subunit Nav1.6 (OMIM #614558) (Veeramah *et al*., 2012). Missense mutations, which have been shown to lead to increased channel activity, are found in 1% of patients with previously unexplained infantile-onset DEE, with more than 100 patients reported (Meisler *et al*., 2016). Mean age at seizure onset is 4-5 months. Most patients present with multiple seizure types, usually not triggered by fever, and can experience various abnormal motor features such as ataxia, dystonia, hyperreflexia, and choreoathetosis. In many cases, development is normal prior to seizure onset, but then slows or regresses. Seizures are mostly pharmacoresistant, but a positive response to sodium channel blockers has been reported. Sudden unexpected death in epilepsy (SUDEP) is reported in about 10% of the cases. EEG features include diffuse background slowing, with focal or multifocal epileptiform abnormalities. MRI brain studies are normal with a few reports of progressive cerebral atrophy (Ohba *et al*., 2014; Blanchard *et al*., 2015; Dyment *et al*., 2015; Larsen *et al*., 2015; Mercimek-Mahmutoglu *et al*., 2015; Boerma *et al*., 2016; Butler *et al*., 2017). Paroxysmal movement disorder, reported in some cases, remains to be clarified (Larsen *et al*., 2015).

We report herein a four-year-old boy presenting with severe non-epileptic movements, possibly of antenatal onset, progressively associated with pharmacoresistant epilepsy and regression, associated with a *de novo* heterozygous missense variant of *SCN8A*.

Case study

Clinical features

The patient was a four-year-old boy born to healthy unrelated parents. He was born at full term (weight: 4,640 g [+1 SD], length: 50 cm [-1 SD], head circumference: 38.5 cm [+3 SD]), without any distress. Since the first hour of life, he presented with moderate stridor and frequent daily tremor episodes, lasting up to 30 seconds, occurring spontaneously or elicited by movement, crying, or acoustic or tactile stimulation. These episodes could also start during quiet sleep and provoked awakening. There was a variable involvement of the head, limbs, diaphragm, and vocal cords. Intensity was variable, always with a crescendo/decrescendo, and without obvious loss of consciousness. Initially, tremor episodes could be stopped by holding the patient. Retrospectively, the mother reported abnormal tremulous foetal movements from the fourth month of pregnancy.

Gradually, tremor episodes became almost continuous at awakening, involving the whole body, and the frequency and amplitude increased with motor activities. At three months of age, the tremor episodes could no longer be stopped by holding the patient, and were progressively associated with axial hypertonia and desaturation provoked by a laryngospasm without fainting that lasted one to five minutes. A first generalised myoclonic seizure was observed. The patient had good eye contact, normal axial tone with only mild peripheral hypertonia between episodes. Pathological startle reflex to nose percussion was observed. Neither Vigevano's manoeuvre (forced flexion of the head and legs towards the trunk) nor clonazepam (maximum: 0.1 mg/kg/day) were effective, making a diagnosis of hyperekplexia unlikely (Vigevano *et al*., 1989; Dreissen and Tijssen, 2012). Only carbamazepine (maximum: 40 mg/kg/day) reduced laryngospasm manifestations. Severe neonatal episodic laryngospasm was ruled out based on normal EMG and *SCN4A* sequencing.

At six months of age, the patient experienced multiple daily epileptic seizures occurring within the continuity of a tremor episode, manifesting as severe tonic whole-body stiffening with apnoea and asystole, requiring mask ventilation. The tonic phase was followed by a bilateral clonic seizure, lasting one to three minutes. Seizures were often serial, not triggered by fever, and were pharmacoresistant, with the exception of carbamazepine (maximum: 40 mg/kg/day) and phenytoin (maximum: 15 mg/kg/day) which reduced the tonic apnoeic component, allowing discontinuation of mask ventilation. Psychomotor development was impaired after six months of age, with axial hypotonia, hyperexcitability, and lack of prehension. Regression was noticed after a convulsive status epilepticus at 18 months of age with loss of ocular contact, massive hypotonia, loss of babbling and swallowing, and poor feeding. Head circumference became progressively small (-0.5 SD). The patient had severe constipation and gastroparesis with daily vomiting, even after gastrostomy. Metabolic screening was normal.

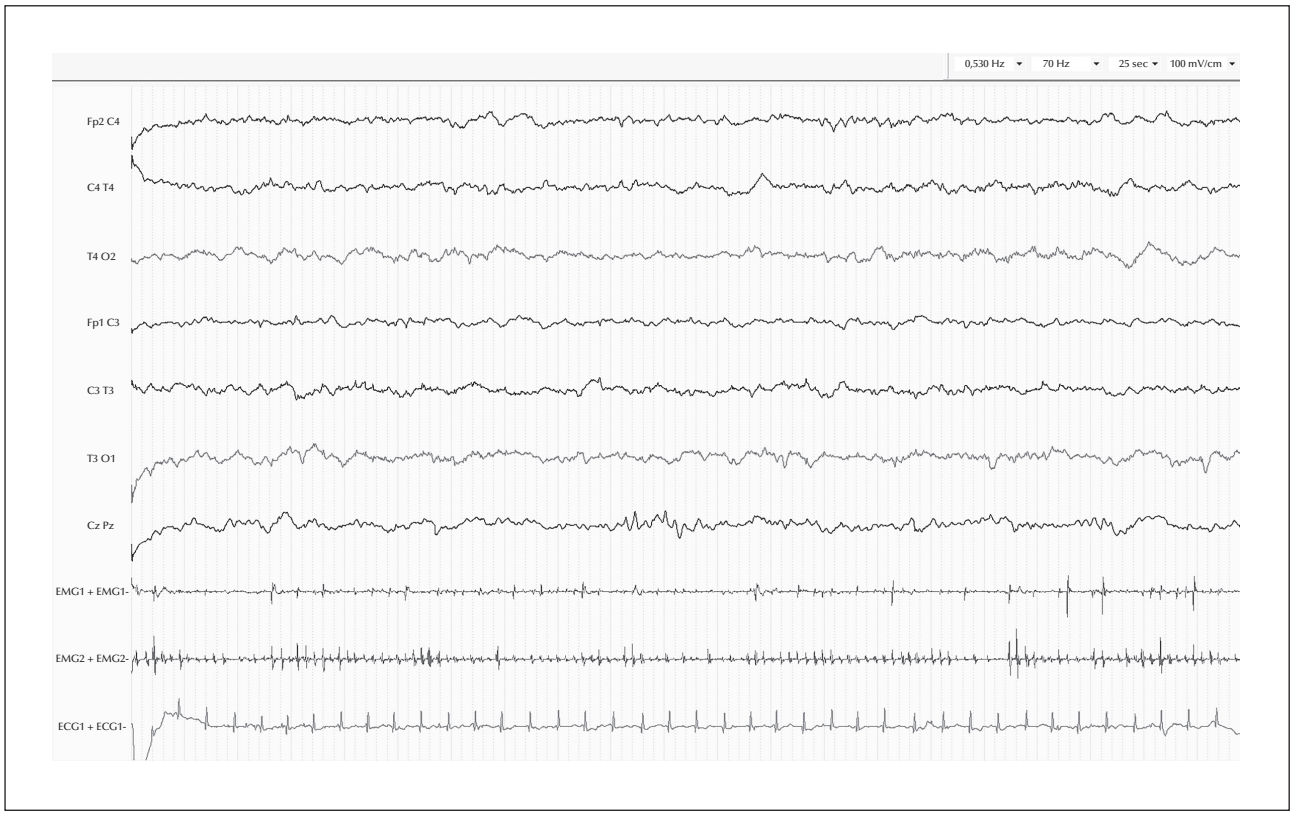

Figure 1. EEG during a tremulous episode at age 12 days showing EMG bursts without corresponding paroxysmal activity (right and left deltoids).

Video-EEG investigations

Neonatal EEGs were normal. Recordings of tremulous episodes showed myoclonic bursts on EMG without any abnormal paroxysmal activity on EEG (*figure 1 and video sequences 1, 2*). Sleep spindles were present at the age of six weeks. At three months of age, multifocal spike and waves appeared during sleep. At six months of age, multiple seizures were recorded with apnoea and asystole (*video sequence 3*). After 18 months of age, diffuse background slowing, multifocal paroxysmal abnormalities, and subclinical bifrontal alpha discharges during sleep were observed.

Neuroimaging

Brain MRI was normal at two days of life, but revealed overall cerebral atrophy at 18 months of age with global rarefaction of white matter and expansion of lateral ventricles and cortical sulci.

Genetic analysis

Multiple parallel sequencing was performed using blood-extracted DNA from the patient with a gene panel including 90 genes involved in monogenic epileptic syndromes (gene list available upon request). After sonication (Covaris, Woburn, MA, USA), library preparation was performed using SeqCapEZ following the manufacturer's recommendations (Roche Nimblegen, Madison, WI, USA). Paired-end 2×75-bp sequencing was performed on a NextSeq500 (Illumina, San Diego, CA, USA). Depth of coverage was over 50x for 99.9% of the targeted regions. Rare variants were considered with a frequency <1% in public databases (ExAC, EVS, and 1000G). A *de novo* heterozygous missense variant of *SCN8A* (Chr12:52183191C>A [hg19]) was identified; c.4408C>A; p.Gln1470Lys (NM_014191.1). To date, this variant has not been reported and is absent from control databases; it was interpreted as a pathogenic variant. The variant was confirmed in the patient by Sanger sequencing and was absent in blood DNA from the parents.

Discussion

We report herein the case of a four-year-old boy presenting with severe non-epileptic tremulous

movements, of possibly antenatal onset, with a marked reflex component and hyperekplexia-like startles, progressively associated with pharmacoresistant epilepsy and regression, associated with a *de novo* heterozygous missense variant of *SCN8A*.

We considered these abnormal movements as multifocal non-epileptic myoclonus, reflecting sensorimotor hyperexcitability. Cortical hyperexcitability was documented on EEG a few months later. Epilepsy became obvious at six months of age with multiple daily life-threatening seizures and apnoea and asystole, requiring mask ventilation, imposing a high risk of SUDEP. Diffuse cortical, subcortical, and peripheral hyperexcitability could be related to the expression of the neuronal sodium channel Nav1.6 encoded by *SCN8A*. Nav1.6 is predominantly expressed in neurons and is widespread throughout the central and peripheral nervous system. Furthermore, *SCN8A* transcripts are readily detected in the prenatal brain (Meisler *et al*., 2016), which could account for the antenatal onset. Singh *et al*. (2015) described a patient with *de novo SCN8A* DEE (c.3979A>G; p.Ile1327Val) with a strikingly similar phenotype involving "drumming" *in utero* movements, exaggerated startle, and jitteriness, which appeared before electroclinical evidence of epilepsy. The same *SCN8A* mutation was reported by Vaher *et al*., associated with neonatal tremor and myoclonias, exaggerated by tactile stimuli, and pharmacoresistant seizures with apnoea and bradycardia (Vaher *et al*., 2014). Interestingly, in their series of 17 *SCN8A* DEE patients, Larsen *et al*. reported one patient with generalised tonic-clonic seizures preceded by apnoea and deep cyanosis, another patient with a reflex component to seizures, and three others with movement disorders, however, coexistence with non-epileptic multifocal myoclonus was not specified (Larsen *et al*., 2015).

Non-epileptic paroxysmal episodes, including startle-like myoclonus or generalized tremor, may be an early feature of some DEE patients with different genetic aetiologies, such as mutation in *STXBP1* (Mignot *et al*., 2011) or *KCNQ2* (Mulkey *et al*., 2017), or non-genetic aetiologies, such as severe hypoxic-ischaemic injury (Walsh *et al*., 2015). These other severe differential diagnoses should be discussed. Moreover, the fact that these manifestations can be triggered by sound or touch is a very important clue for differential diagnosis with epileptic seizures other than the EEG ictal findings.

Precise determination of tremulous movements can be challenging in neurophysiological phenotyping. To define a phenomenon as a tremor, a common method in EEG-EMG polygraphy is to record EMG activity from agonists and antagonists (for myoclonus, the contraction is simultaneous in both muscles, whereas for tremor it alternates between the two). Furthermore, a clinical phenomenon resembling a tremor was in fact reported to be a cortical phenomenon based on appropriate methods, such as measuring EEG-EMG coherence (Brown *et al*., 1999; Panzica *et al*., 2003; Canafoglia *et al*., 2006; Rubboli *et al*., 2011). Unfortunately, in our case, neither recording of agonists/antagonists, nor back-averaging or other specific methods could be performed.

The association between severe perinatal non-epileptic multifocal reflex myoclonus and seizures with a striking vegetative component may represent a recognisable phenotype within a subgroup of *SCN8A* DEE patients. Clinicians should be aware of these features in order to establish rapid diagnosis. This is essential because of the risk of life-threatening complications and the positive effect reported with sodium channel blockers in some patients (Larsen *et al*., 2015; Boerma *et al*., 2016).

In conclusion, this report highlights that paroxysmal non-epileptic episodes of severe tremor and hyperekplexia-like startles and a striking vegetative component can be the first symptoms of severe *SCN8A* DEE. These symptoms should be recognised in patients in order to avoid misdiagnosis and ensure early appropriate therapeutic management. □

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None of the authors have any conflict of interest to declare.

Legend for video sequences

Video sequence 1.

Tremulous episode.

Video sequence 2.

Multifocal myoclonia without corresponding EEG.

Video sequence 3.

Seizure with apnoea and asystole.

Key words for video research on www.epilepticdisorders.com

Phenomenology: tremulous episode (video 1), multifocal myoclonia without EEG correspondence (video 2), seizure with apnoea and asystole (video 3)
Localization: not applicable
Syndrome: SCN8A EE
Aetiology: non epileptic paroxysmal disorders

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TEST YOURSELF

(1) Which of the following manifestations can be seen in early-onset *SCN8A* developmental and epileptic encephalopathy?

A. Abnormal tremulous-like foetal movements
B. A reflex component to a seizure
C. Macrocephaly
D. Seizures with apnoea and asystole

(2) Which of the following manifestations are not seen in early-onset *SCN8A* developmental and epileptic encephalopathy?
A. Neonatal tremor episodes
B. Hyperekplexia-like presentation
C. Typical facial dysmorphisms
D. SUDEP

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".