■ Clinical commentary

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Epileptic Disorders

Paroxysmal tonic upgaze in a child with SCN8A-related encephalopathy

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ABSTRACT – Pathogenic variants in the *SCN8A* gene have been associated with a broad phenotypic spectrum, ranging from benign familial infantile seizures to severe, early-onset developmental and epileptic encephalopathy. This spectrum also includes an "intermediate phenotype" characterized by different degrees of cognitive disability, mild neurological impairment, and therapeutically manageable epilepsy. We report on a child harbouring a *de novo*, novel *SCN8A* deletion, whose clinical picture is consistent with an *SCN8A*-related "intermediate phenotype". This patient's peculiar feature is the occurrence of paroxysmal tonic upgaze (PTU), a non-epileptic disorder consisting of sustained conjugate upward deviation of the eyes, with neck flexion, and downbeat saccades. PTU has been described in otherwise healthy children, as well as in a few genetic syndromes, but has never been observed in *SCN8A*-related phenotypes. This report, therefore, adds a new symptom to the spectrum of movement disorders associated with *SCN8A*-related developmental and epileptic encephalopathy. In this short communication, we provide video-EEG documentation of PTU and seizures, and discuss the challenging differential diagnosis between the two symptoms.

Key words: paroxysmal tonic upgaze, paroxysmal movement disorders, *SCN8A*-related epilepsy, DEE, developmental and epileptic encephalopathy

VIDEO ONLINE

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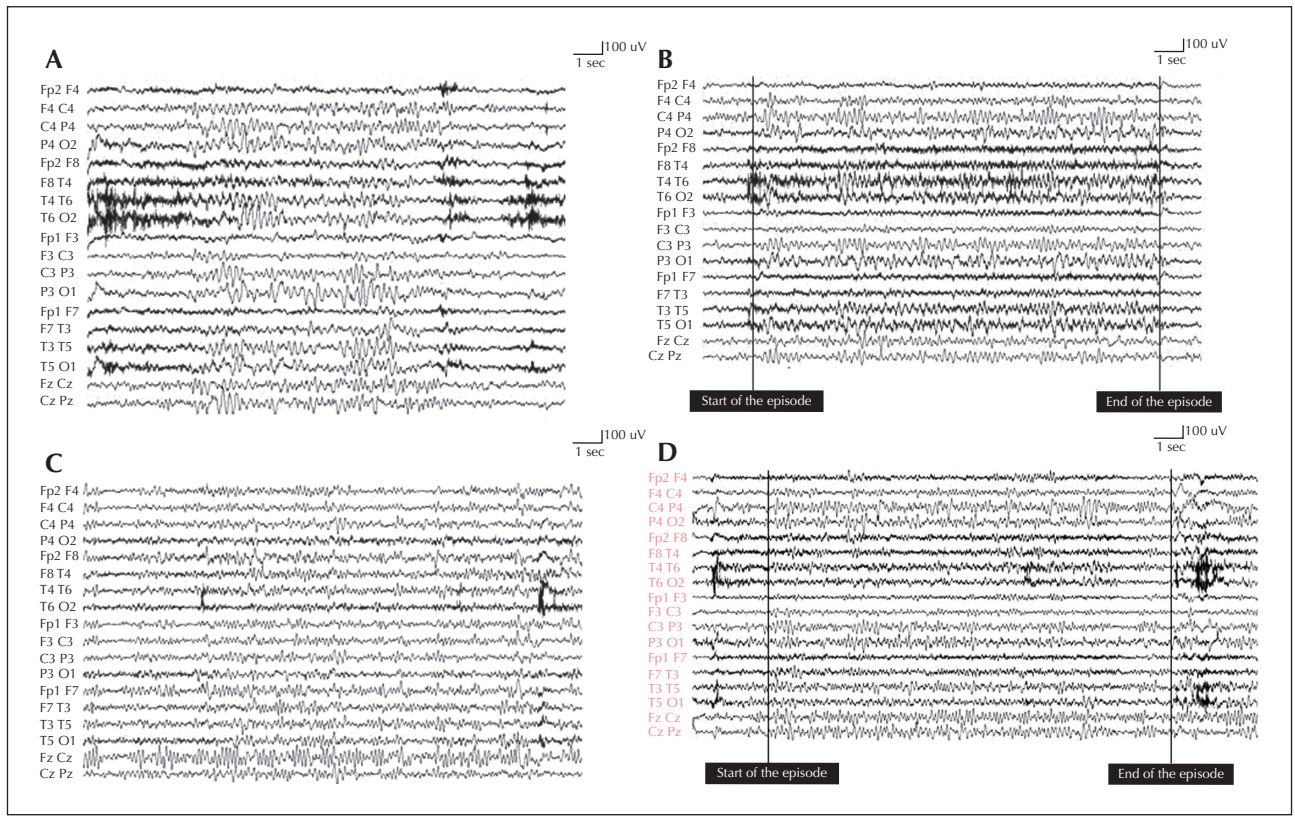
The *SCN8A* gene encodes the alpha subunit of Nav1.6, one of the voltage-gated sodium channels widely expressed in the brain. The main symptoms associated with pathogenic variants of *SCN8A* are epilepsy, movement disorders, and intellectual disability. The phenotypic spectrum is broad, ranging from benign familial infantile seizures (BFIS), in a small number of cases, to more frequently reported severe, early-onset developmental and epileptic encephalopathy (DEE) [1, 2]. In several patients (28% according to Gardella and Moller [2]), the disease features an "intermediate phenotype". In these patients, cognitive disability, hypotonia, movement disorders, and ataxia are present, but these symptoms are less invalidating than in the severe phenotype (for example, walking is often preserved), moreover, seizures are drug responsive in about half of cases [2, 3].

Paroxysmal tonic upgaze (PTU) is an involuntary, non-epileptic disorder, consisting of sustained conjugate upward deviation of the eyes, neck flexion, and downbeat saccades. This phenomenon was firstly described in otherwise healthy children as a benign phenomenon that disappears during infancy in most cases [4-7]. PTU has been reported in children with developmental delay or ataxia of unknown aetiology, and in a few



■ **Figure 1.** Polygraphic recordings performed at 2.5 years (upper panels) and 3.5 years (lower panels), during wakefulness (A, C) and during PTU (B, D). A) The background activity is intermingled with sequences of posterior 3.5-4-Hz waves. C) Background activity is characterized by 5-Hz rhythm, poorly reactive to eye opening. B, D) EEG during two episodes of PTU; the lines mark the onset and the end of the episodes. In both cases, the EEG is very similar to the "interictal" EEG shown in *figure 1A, C*. At 2.5 years, posterior 3.5-Hz activity, lasting 17 seconds, is evident (B), and at 3.5 years,the intermittent appearance of posterior 5-Hz activity is seen during the episode (D).

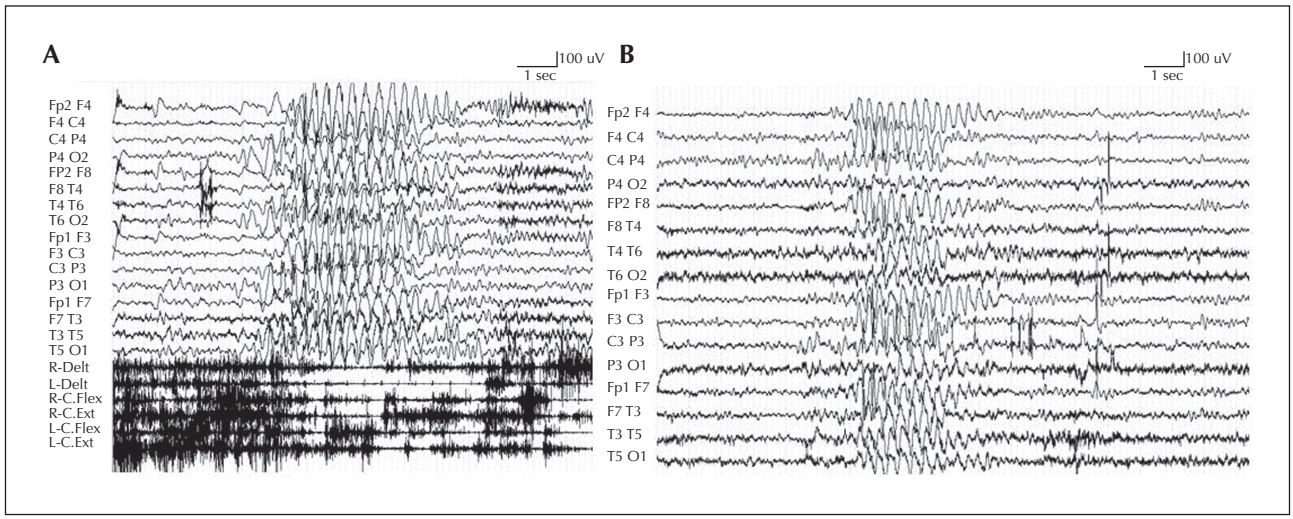
children with genetically defined diseases, namely in encephalopathies associated with pathologic variants of *CACNA1A*, *GRID2* and *SEPSECS* and in a case of partial tetrasomy of chromosome 15 [8-10].

We report a case of a child harbouring a pathological variant of *SCN8A*, in whom PTU was a predominant symptom of a clinical picture consistent with the *SCN8A*-intermediate phenotype.

Case study

The 3.5-year-old boy was the only child of non-consanguineous parents. He was born at term after normal pregnancy and delivery. Family history was unremarkable, as was his personal early medical history. At the age of eight months, motor delay became evident. He walked at the age of 15 months; since then, gait was uncertain with frequent falls.

The boy experienced a first seizure at the age of 14 months, during fever; the seizure was characterized by increased muscle tone of the upper limbs, followed by bilateral myoclonic jerks. Similar seizures associated with fever recurred in the following few months. At that time, the interictal EEG was normal. The frequency of attacks progressively increased and recurred monthly, also in the absence of fever. At 20 months, the boy started experiencing different brief paroxysmal events characterized by sustained, conjugate upward eye deviation, usually associated with slow flexion of chin and trunk and interruption of motor activity. Ten months later, at the time of our first observation, these episodes recurred several times a day. EEG during wakefulness was characterized by posterior theta rhythm (5-6 Hz) and interictal sequences of posterior 3.5-4-Hz waves, lasting 2-10 seconds, without concomitant changes in behaviour



■ **Figure 2.** Polygraphic recordings performed at 3.5 years, revealing two episode of "absence" seizures; in both cases, the briefabrupt interruption of motor activity (visible on the EMG traces in *figure 2A*) correlates with a diffuse 2.5-3-Hz spike-and-wave discharge, predominant on anterior regions. R: right, L: left; Delt: deltoid muscles; C: flex; C. Ext: flexor and extensor carpi.

(*figure 1A*). During sleep, focal occipital spikes and interictal sequences of 2-Hz diffuse high-voltage spike and waves were observed. We were unable to record myoclonic seizures. By contrast, we recorded several episodes of impaired awareness and conjugate tonic upward eye deviation; the concurrent EEG did not show ictal changes (*figure 1B, video sequence 1 [part 1]*). Valproate treatment reduced the frequency of myoclonic seizures, but not that of upward eye deviation.

One year later, the video-EEG confirmed the presence of non-epileptic phenomena, consisting of slow flexion of the trunk and chin, conjugate tonic upward eye deviation, and reduced motor activity (*figure 1D, video sequence 1 [part 3]*). Moreover, EEG showed seizures characterized by a brief loss of contact associated with a 2.5-Hz spike-wave discharge lasting 5-7 seconds (*figure 2, video sequence 1 [part 2]*).

The video EEG recordings documented the co-occurrence of epileptic and non-epileptic paroxysmal events, namely "absence" seizures and PTU. Adding lamotrigine to valproate led to disappearance of myoclonic seizures and "absences" but did not modify the frequency of PTU.

During the follow-up, gait ataxia and microcephaly became evident. The cognitive evaluation showed moderate intellectual disability (GQ 51 based on Griffith's scale). Brain MRI, at 2 and 3.5 years of age, only showed mega-cisterna magna.

The following genetic investigations were unrevealing: array CGH, chromosome 15 methylation test and *SLC2A1* gene analysis. Next-generation sequencing (NGS) analysis of a panel containing 243 genes related to epileptic encephalopathies and myoclonus epilepsies detected the presence of a heterozygous in-frame deletion in the *SCN8A* gene (c.1229_1237delTGGCCATGG). Segregation analysis excluded the presence of this variant in both parents. This is therefore a novel *de novo* variant, which determines an "in frame" deletion of nine nucleotides and three amino acids (p.Val410_Met412del) of the ion transport domain of the protein. This variant has not been reported in gnomADexome or gnomADgenomedatabase (http://gnomad.broadinstitute.org/) and is classified as Class 3 according to the American College of Medical Genetics and Genomics guidelines (ACMG). However, this variant is classified as likely pathogenic based on the VarSomeClinical database (https://www.varsome.com/), moreover, the deletion falls within the hotspot of 72 basepairs comprising five other variants reported as pathogenic.

Discussion

Epileptic seizures and movement disorders are key symptoms of *SCN8A*-related syndromes [1].

We report a patient with an *SCN8A*-intermediate phenotype, characterized by mild developmental delay, drug-responsive myoclonic and "absence" seizures, and multiple brief episodes of a peculiar movement

disorder consistent with paroxysmal tonic upgaze. The co-existence of "absences" and PTU challenged the differential diagnosis between an epileptic event and a paroxysmal movement disorder. The psychomotor arrest associated with PTU, and its short duration, together with the presence of frank seizures, and the presence of interictal EEG epileptic activity, initially led to misdiagnose PTUs as seizures. Only the careful re-evaluation of the video-EEG recordings of several episodes clarified that the conjugate tonic upward deviation was associated with sequences of posterior delta or theta rhythms, similar to that frequently intermingled with the child's background activity and not with any ictal pattern. The non-epileptic origin of PTU was also supported by complete insensitivity to ASMs that, by contrast, led to the disappearance of "absences" and myoclonic seizures.

As already mentioned, movement disorders are almost invariably present in *SCN8A*-related syndromes. Dystonia, choreo-atetosis, and myoclonus are mainly observed in the "severe DEE phenotype" [1], whereas paroxysmal dyskinesias have been described in association with BFIS [11], and more recently in patients with the "intermediate phenotype" [3]. As far as we know, PTU has never been reported.

The anatomical substrate and physiopathology of PTU are still unclear. PTU has been described as a benign and transient phenomenon in otherwise healthy children, but also frequently associated with ataxia in pathological conditions such as structural brain lesions, neurotransmitter disorders, and *CACNA1A* channelopathy [4-10]. In the latter disease, cerebellar dysfunction, impairing the cortico-ponto-cerebellar-thalamo-cortical pathway,has been advocated as the physiopathological mechanism [9].

Both *CACNA1A* and *SCN8A* genes are widely expressed in the brain, both in the cortex, subcortical structures, and the cerebellum. In our patient, the presence of ataxia further supports the role of cerebellar dysfunction and the cortico-ponto-cerebellar-thalamo-cortical pathway in the genesis of PTU.

In conclusion, this report broadens the spectrum of movement disorders associated with *SCN8A*-related DEE, to possibly include this condition in a child presenting with PTU, epilepsy and intellectual disability. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
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Legend for video sequence

Part 1: at the age 2.5 years, paroxysmal tonic upgaze deviation associated with slow flexion of the chin and trunk and interruption of motor activity; Part 2: at the age 3.5 years, absence seizure; Part 3: at the age 3.5 years, paroxysmal tonic upgaze associated with flexion of the chin and interruption of motor activity.

Key words for video research on www.epilepticdisorders.com

Phenomenology: absence (dialeptic) seizure, nonepileptic paroxysmal event
Localization: not applicable
Syndrome: epilepsy not classified
Aetiology: genetic disorder

TEST YOURSELF

(1) What is paroxysmal tonic upgaze?

(2) How many epileptic phenotypes are associated with SCN8A gene mutation?

(3) Are paroxysmal movement disorders reported in SCN8A-related syndromes?

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".