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Brief Communication

Generalized tonic seizures with autonomic signs are the hallmark of *SCN8A* developmental and epileptic encephalopathy

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ABSTRACT

Developmental and epileptic encephalopathy (DEE) due to *SCN8A* gene variants is characterized by drug-resistant early onset epilepsy associated with severe intellectual disability. Different seizure types have been reported, and a sequence of autonomic manifestations such as brady-/tachycardia, irregular breathing, and cyanosis. Nevertheless, an exhaustive video-polygraphic documentation is still lacking. In this study, we reviewed the ictal electroencephalograms (EEGs) of five patients with *SCN8A*-DEE followed-up at the Neuroscience Department at Bambino Gesù Children's Hospital in Rome. We identified generalized tonic seizure as the major seizure type at epilepsy onset. Seizure severity could vary from subtle to marked clinical manifestations, depending from the extent and groups of muscles involved and association with autonomic modifications. We found autonomic signs in 80% of seizures in our cases, and we were able to identify a stereotyped sequence of ictal events for most of seizures. Autonomic signs occurred in rapid sequence: flushing of the face, sometimes associated with sialorrhea, bradycardia, and hypopnea appeared within the first 1–2 s. Tachycardia, polypnea, perioral cyanosis, and pallor occurred later in the course of the seizure.

Generalized tonic seizures are rarely described in other genetic epileptic conditions of early infancy because of ion channel mutations, such as in DEE due to *KCNQ2* or *SCN2A* gene mutations, where seizures are most frequently reported as focal to bilateral tonic. Therefore, generalized symmetric tonic seizures with autonomic signs can be considered a clinical hallmark for diagnosis of *SCN8A*-related DEE and relevant for therapeutic implications.

1. Introduction

SCN8A-related developmental and epileptic encephalopathy (DEE) (EIEE13, OMIM #614558) is a recently recognized epileptic syndrome caused by de novo *SCN8A* variants. During the last years, the electroclinical phenotype in patients with *SCN8A*-related DEE has been accurately reported [1]. It is characterized by seizures with onset before 18 months of age, with different types of seizures including focal, generalized, and more rarely epileptic spasms. Epilepsy is drug-resistant, although seizure frequency may improve with sodium channel-blockers antiepileptic drugs (AEDs) [2]. Developmental impairment is usually severe, and often is associated with pyramidal and extrapyramidal signs [1,3].

Interictal electroencephalogram (EEG) shows a progressive slowing of background activity together with multifocal epileptiform abnormalities, mainly over the temporal–parietal–occipital regions. Ictal EEG consists of posterior temporal rhythmic activity or diffuse EEG desynchronization. Clinical correlate is mainly characterized by hypomotor and autonomic signs, followed by motor manifestations (tonic, tonic-vibratory, clonic or hemiclonic, tonic–clonic) [1]. Autonomic symptoms occurring during seizures, such as brady-/tachycardia, irregular breathing, and cyanosis, are commonly reported: they are considered as risk factors for ictal death [1].

The aim of this study was to review ictal EEGs in a series of patients with *SCN8A*-DEE and provide a video-polygraphic documentation of seizures and autonomic signs in order to better clarify the underling neurophysiological mechanisms. Moreover, the chance to identify a stereotyped seizure phenomenology might allow early diagnosis and could have therapeutic implications, considering responsiveness of *SCN8A*-mutated patients to sodium-channel blocker drugs.

2. Material and methods

We reviewed all consecutive ictal EEGs of five patients with *SCN8A*-DEE followed at the Neuroscience Department at Bambino Gesù Children's Hospital in Rome. Few clinical features of four (Pts #1, #3, #4, #5) out of five patients were already reported [1]. We reviewed all medical charts, and we collected data on seizure semiology, interictal EEG, treatments, neurological examination, genetic, and brain magnetic resonance imaging (MRI) findings (Table 1). All patients presented with the clinical phenotype of *SCN8A*-DEE recently reported [1], with onset of seizures between

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Table 1
Electroclinical, genetic, and neuroimaging data of patients with *SCN8A*-DEE.

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5
Sex/age at study	M/3 y	F/10 m	F/3 y	F/9 y	M/11 y
Age at seizure onset	4 m	40 d	21 d	3 m	1 m
Seizure types (age of onset)	TS (4 m), FS (5 m), TCS (2 y8 m)	TS (40 d), myoclonic (6 m)	TS (21 d)	TS (3 m), FS (5 m), TCS (2 y)	FS (1 m), TS (2 m), hemiclonic (6 y)
Interictal EEG (last FU)	Occipital bilateral slow waves	Occipital bilateral slow waves	Slow background activity. F-T asynchronous spikes.	Slow background activity. Bilateral F delta waves.	Slow background activity. Bilateral occipital slow waves.
Number of recorded seizures	1	16	4	1	3
Age at ictal EEG	4 m	50 d	4 m, 19 m	18 m	1 m
Types of recorded seizure	1 tonic	15 tonic, 1 focal	2 tonic, 2 focal	1 focal to bilateral	3 hemiclonic
Developmental at follow-up	Moderate ID	Mild ID	Severe ID	Severe ID	Severe ID
Treatment	(+) PHT, CBZ (−) LEV	(+) PHT, CBZ (−) PB	(+) PHT, MDZ (SE); (−) CBZ, LZP, VPA, LEV, LCS, PB, CBD	(+) CBZ, PHT, PRM, prednisone; (−) LEV, LCS, STP, PB, TPM, ZNS, KD	(+) CBZ, PHT; (−) LEV, TPM, PB
Brain MRI	Normal (10 m)	Normal (2 m)	Cortical and subcortical atrophy mainly over frontal and parietal regions, CC hypoplasia, severe cerebellar atrophy (18 m)	F cortical atrophy, moderate cerebellar atrophy mainly over frontal regions (6 y)	Diffuse cerebral and cerebellar atrophy (6 y)
SCN8A variant	c.4423G > A, p.GLy1475Arg	c.4410A > C, p.Gln1470His.	c.4472C > T, p.Ala1491Val	c.4948G > A, p.Ala1650Thr	c.2590C > G, p.Leu864Val

M = male; F = female; m = months; d = days; ID = intellectual disability; TS = tonic seizure, TCS = tonic–clonic seizure; FS = focal seizures; F = frontal; T = temporal; PHT = phenytoin; CBZ = carbamazepine; PB = phenobarbital; MDZ = midazolam; LEV = levetiracetam; LZP = lorazepam; PRM = primidone; STP = stiripentol; LCS = lacosamide; CBD = cannabidiol; TPM = topiramate; ZNS = zonisamide; KD = ketogenic diet; FU = follow-up; + = effective drug; − = not effective drug.

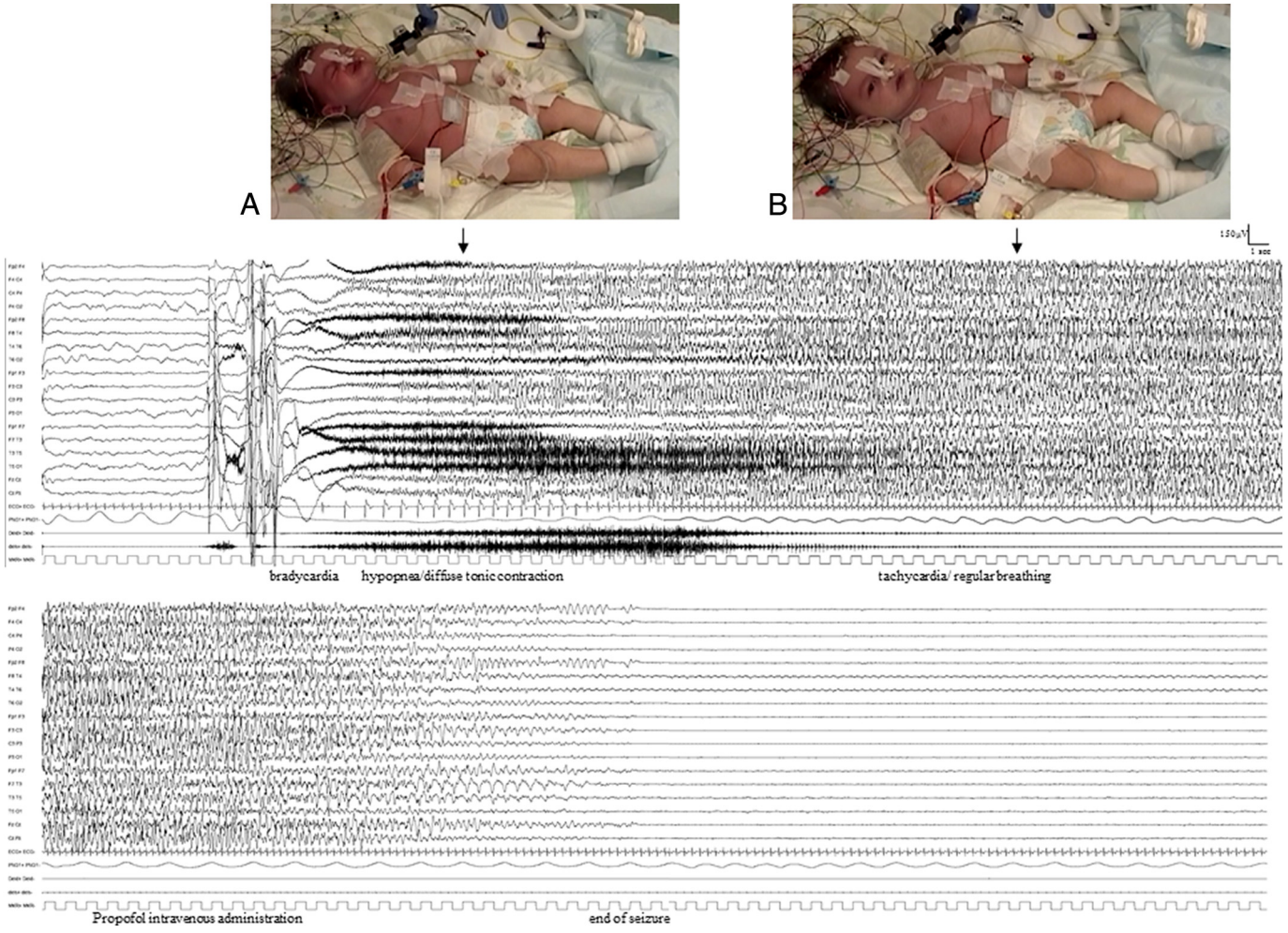

Fig. 1. Ictal video-polygraphic recording of a 4-month-old boy (case #1). The ictal discharge starts with a diffuse low-voltage fast activity, increasing in amplitude and decreasing in frequency, bilateral and symmetrical. Video-frame A shows a massive tonic contraction with flushing of the face and trunk, perioral cyanosis, and sialorrhea. Polygraphic recording shows ictal bradycardia (35 bpm) at seizure onset. Hypopnea is concomitant with bradycardia, and lasts for 9 s, for the whole duration of the tonic phase (see the bilateral contraction of upper limbs on deltoids). Afterwards, there is a hypotonia and pallor (video-frame B) associated with compensative tachycardia (180 bpm) and the reappearance of a regular breathing. Seizure ends after 82 s with intravenous propofol administration. **Permission granted for photos**.

the age of 3 weeks and 4 months. Seizures were tonic, focal, focal to bilateral, clonic/hemiclonic, and generalized tonic–clonic. All patients had intellectual disability (from mild to severe) and drug-resistant epilepsy, although three of them reached a good seizure control with the occurrence of sporadic annual seizures, after the introduction of sodium-blocker channel drugs. All seizures were video-EEG recorded with polygraphic channels including bilateral deltoids electromyography (EMG) and electrocardiogram (ECG). Thorax-breathing was recorded in all seizures except four. Seizures were classified according to the current International League Against Epilepsy (ILAE) seizure classification [4]. For each patient, we recorded different types of seizures, and therefore, we grouped them according to their semiology. This study was conducted according to appropiate ethical standards as required by the Ethic Committee of Bambino Gesù Children's Hospital.

3. Results

We reviewed a total number of 25 seizures (Supplementary Table 1). All recorded seizures occurred between the age of 4 and 19 months. Main type of seizure (n = 18) was generalized tonic with autonomic signs: this was reported in all *SCN8A*-mutated patients and video-EEG recorded in three patients (Pts #1, #2, #3) (Figs. 1–3). During follow-up, 4 out 5 patients developed other seizure types. Recorded seizures at follow-up (n = 7) were distinguished into focal (n = 3), hemiclonic (n = 3), and focal to bilateral (n = 1), and occurred in patients #2, #3, #4, #5 (Table 1).

Generalized tonic seizures were characterized by a similar sequence of ictal clinical manifestations (Supplementary Table 1). Seizures' onset was typically with a sudden generalized hypertonia, intense and massive muscle contraction involving mainly axial and abdominal muscles, and symmetrically the four limbs. During this tonic phase, autonomic signs, such as flushing, bradycardia (down to 25 bpm) and/or tachycardia (up to 180 bpm), sialorrhea, perioral cyanosis, pallor, and hypoapnea, were evident. In all seizures except one, bradycardia preceded tachycardia. Sialorrhea was often concomitant with flushing. Perioral cyanosis and pallor occurred later during the course of seizures (Figs. 1–3). Seizure duration was variable, from 15 to 200 s, and all but one had a spontaneous remission.

The other seizure types (n = 7) had different semiology (focal, hemiclonic, and focal to bilateral), and only rarely (n = 2), they were associated with autonomic signs (flushing and tachycardia to 180 bpm). The EEG counterpart of generalized tonic seizures was characterized by a diffuse low-voltage fast activity followed by bilateral and symmetrical theta rhythms.

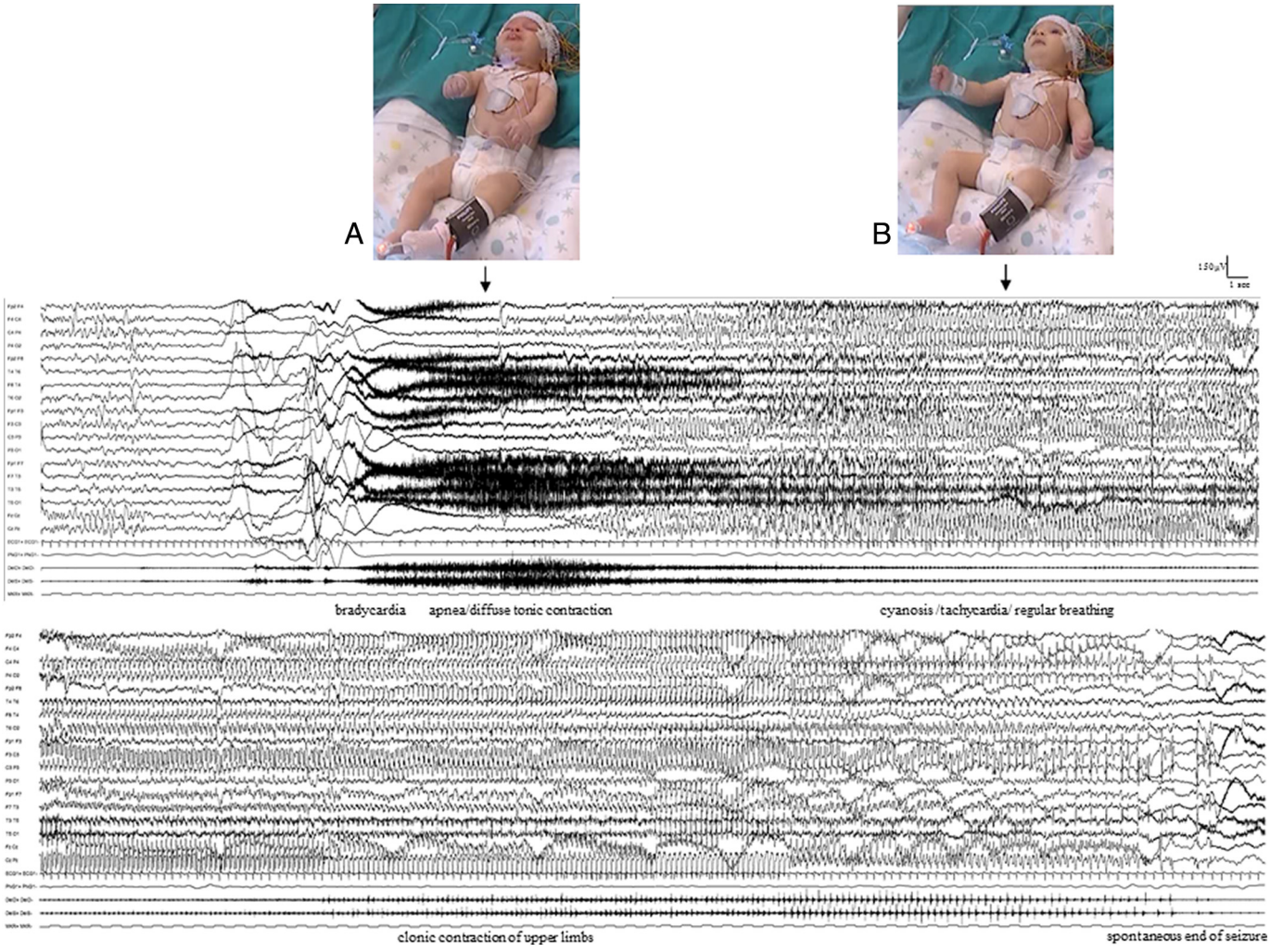

Fig. 2. Ictal video-polygraphic recording of a 50-day-old girl (case #2). The ictal discharge starts with a diffuse low-voltage fast activity, increasing in amplitude and decreasing in frequency, bilateral and symmetrical. Video-frame A shows a massive tonic contraction with flushing of the face and sialorrhea. Polygraphic recording shows ictal bradycardia at seizure onset (60 bpm). Hypopnea is concomitant with bradycardia, and lasts for 16 s, for the whole duration of the tonic phase (see the bilateral contraction of upper limbs on deltoids). Afterwards, there is a clonic contraction, associated with pallor of the face and perioral cyanosis (video-frame B) associated with compensative tachycardia (180 bpm) and the reappearance of a regular breathing. Seizure spontaneously ends after 113 s. **Permission granted for photos**.

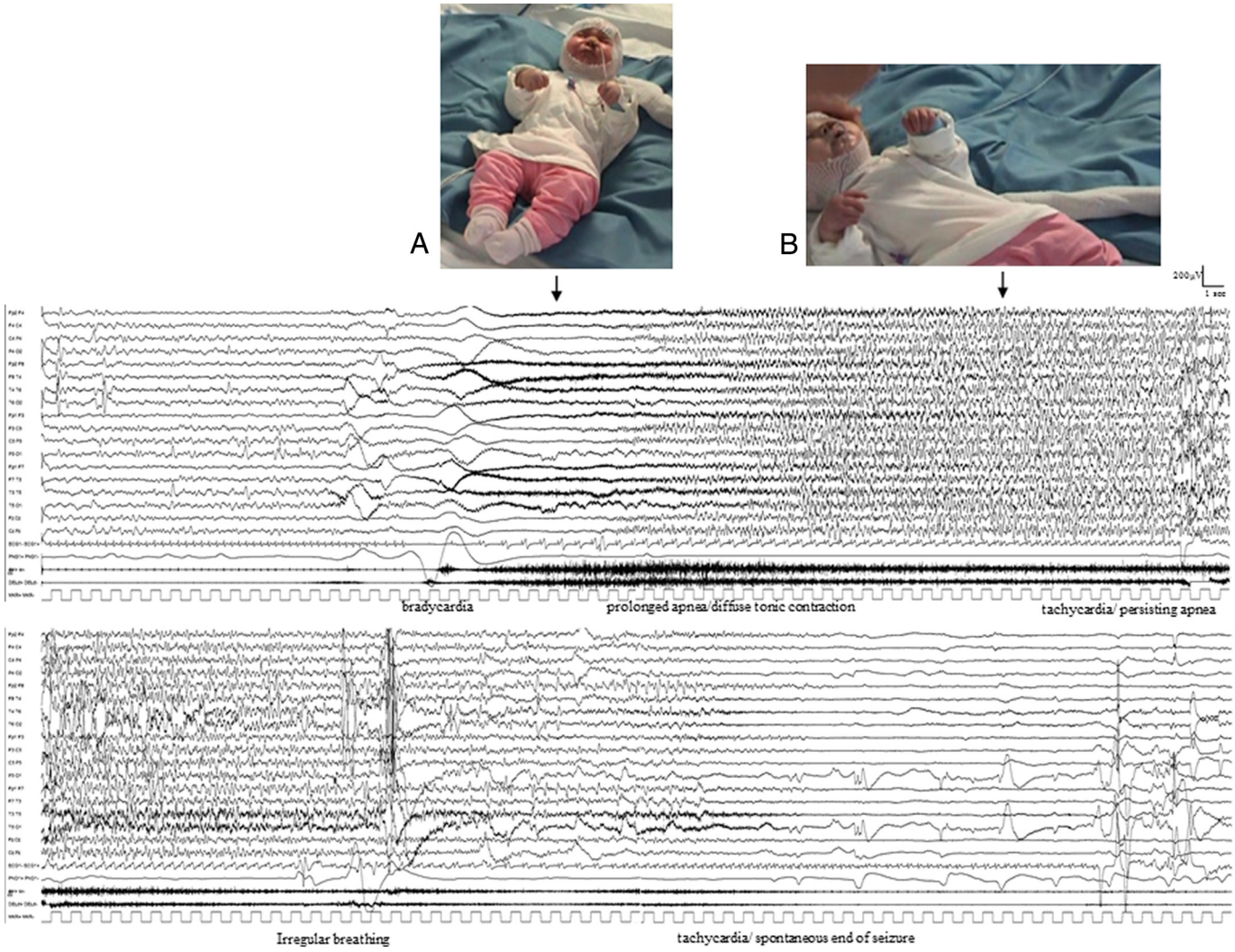

Fig. 3. Ictal video-polygraphic recording of a 4-month-old girl (case #3). The ictal discharge starts with a diffuse low-voltage fast activity, increasing in amplitude and decreasing in frequency, bilateral and symmetrical. Video-frame A shows a massive tonic contraction with flushing of the face, perioral cyanosis, and sialorrhea. Polygraphic recording shows ictal bradycardia (25 bpm) at seizure onset. Hypopnea is concomitant with bradycardia, and lasts for 50 s, for the whole duration of the tonic phase (see the bilateral contraction of upper limbs on deltoids). Afterwards, there is a slight reduction of hypertonia associated with pallor of the face and perioral cyanosis (video-frame B) tachycardia (175 bpm) and the reappearance of a regular breathing. Seizure spontaneously ends after 85 s. **Permission granted for photos**.

Interictal EEG was not specific, showing a slowing background activity and bilateral posterior slow waves in all five patients. Epileptiform frontal and temporal spikes were found in one patient (Table 1).

4. Discussion

This study allowed us to identify generalized tonic seizure as the major type of seizure in *SCN8A*-related DEE at onset. Generalized tonic seizures are described as event with symmetrical sustained increase in muscle contraction, usually lasting from few seconds to 1 min [5]. Severity could vary depending on the extent and groups of muscles involved. In this spectrum of seizure severity, in *SCN8A*-mutated patients, muscles' contraction is quite strong and sustained and associated with ictal autonomic modifications. We used the term "tonic" to define this seizure type because the diffuse tonic contraction, massive and sustained, is the main clinical feature of the event. In some patients, the tonic phase might be followed by bilateral asynchronous clonic jerks, this does not appear as the typical tonic–clonic seizure seen in adult patients. The muscle contraction seen on EMG channels, preceding the tonic phase (Figs. 1–3), at seizure onset, corresponds to an afinalistic movement of upper limbs on the video recording. Nevertheless, the EMG trace could be misleading for epileptic spasms, which is not the case. Autonomic signs have been described in *SCN8A*-related DEE, and they are mainly characterized by flushing, heart rate variability (tachycardia and/or bradycardia), apnea, and cyanosis [1]. In our series, autonomic signs were found in 80% of seizures, mainly in generalized tonic seizures, although in focal seizures, may also occur. The sequence of ictal clinical manifestations appeared to be stereotyped in all documented generalized tonic seizures. Autonomic signs usually occurred in rapid sequence: within 1–2 s, flushing of the face, sometimes associated with sialorrhea, bradycardia, and hypopnea appeared. Tachycardia, polypnea, perioral cyanosis, and pallor occurred later in the course of the seizure.

Ictal bradycardia is a rare phenomenon, reported in about 8% of pediatric epilepsies [6], and usually is due to hypoxic mechanisms. In our series, the concomitant occurrence of bradycardia and hypopnea at the beginning of the seizure, and during the massive tonic phase, allowed us to hypothesize that bradycardia could be due to the intense contraction of the abdominal muscles. During the tonic phase, patients seemed to present with a Varsalva Maneuver: our cases had a forced expiratory effort against a closed airway (e.g., closed mouth and nose) as first sign of seizure (Figs. 1–3), and during this phase, there was a decrease of heart rate and flush of the face; afterward, pallor and tachycardia as reported in the physiopathology of Varsalva Maneuver [7,8].

Ictal bradycardia was also supposed to be one of the possible risk factors leading to death in *SCN8A*-related DEE. *SCN8A* gene encodes for Nav1.6 channel, and other than in human brain, it is expressed in heart tissue [9], where it is supposed to regulate excitation–contraction coupling and studies. Mouse model of *SCN8A*-DEE has been reported to have hyperexcitability of heart cells exhibiting cardiac arrhythmia, abnormal heart contraction, and cardiac arrest after a progressive worsening of convulsive seizure frequency [10]. Nevertheless, looking at literature, the reported risk of sudden unexpected death in epilepsy (SUDEP) in *SCN8A*-DEE ranged from 10% [11] to 1.6% [12]: it was clarified that not all deaths are due to SUDEP, and mortality due to neurologic deterioration and uncontrolled seizures accounts for about 5.3% [12].

Generalized tonic seizures were also reported by parents, both at onset and during follow-up. During follow-up, seizures usually become less intense with antiepileptic medication, and other seizure types might appear.

This seizure type is rarely described in genetic epileptic condition of early infancy. In DEE with earlier onset (mainly neonatal) due to ion channel mutations, such as *KCNQ2* or *SCN2A* gene variants, mostly focal sequential seizures have been reported [13]. They are characterized by focal manifestations, typically occurring in a sequence, often with changing lateralization within or between seizures. Focal seizures frequently evolve in focal to bilateral tonic seizures in those cases and are characterized by tonic asymmetrical posture with clonic eye jerking and desaturation [14,15]. In *KCNQ2-SCN2A* DEEs, hypertonia usually does not appear so massive and intense as in *SCN8A*-DEE, and rarely is associated with autonomic signs. Lastly in *KCNQ2*-DEE, heart rate abnormalities were reported in about 5% (n = 6/84) of patients, and a different sequence of ictal signs has been reported [14].

5. Conclusions

This study provides a unique EEG-polygraphic documentation of ictal manifestations in *SCN8A*-related DEE, mainly focusing on generalized tonic seizures. Autonomic signs are quite prominent and occur in a rapid sequence at the beginning of seizures, most probably related to massive muscles contraction. In patients with uncontrolled seizures, the occurrence of autonomic ictal signs could be a dangerous combination and might lead to an increased risk of death. As this type of seizures occur during first months of life, it might be considered a clinical hallmark for early diagnosis and allow an optimization of treatment with of sodium-channel-blockers AEDs that could represent a chance in order to reach seizure control.

Conflict of interest

All authors declare no conflicts of interest.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.03.043.

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