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Clinical letter

"Breath holding spells" in a child with SCN8A-related epilepsy: Expanding the clinical spectrum

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1. Text

A 14-month-old, developmentally-normal girl presented with daily events since 6-months of age. The events were characterized by crying (provoked by fall/anger) followed by cessation of crying, peri-oral cyanosis, and tonic stiffening of the limbs and jerking. She also had a microcytic/ hypochromic anemia. Initially she was diagnosed with breath-holding spells with reflex-anoxic seizures and started on iron with no effect. Subsequently, these episodes started happening without crying. On suspicion of seizures, she received phenobarbital and levetiracetam (minimal response) and then oxcarbazepine. After adding oxcarbazepine, the episodes markedly reduced (once/month) and she is now seizure free for 2 months.

Magnetic-resonance-imaging (MRI) of the brain demonstrated high T2 signal in the white matter of the left anterior temporal lobe, suspicious for focal cortical dysplasia type I. Positron-Emission-Tomography was concordant. Video-EEG captured generalized seizures (induced by breath-holding and spontaneous) with unclear lateralization (Video 1). Rarely, sharply contoured slow waves were seen in the left temporal region. Magneto-encephalography revealed occasional spike dipoles (without EEG spikes) over the left posterior insula and posterior portion of left superior temporal gyrus. Targeted epilepsy gene panel revealed a de novo previously described pathogenic variant [c.5630 A > G, p.Asn1877Ser (N1877S)] in the SCN8A gene, which has been associated with milder phenotypes [1]. She is being managed medically at the moment. Epilepsy surgery may be considered in future if she develops drug-resistant focal seizures.

2. Discussion

SCN8A-related epilepsy presents with a variable phenotype from benign infantile seizures to a severe epileptic encephalopathy. The epilepsy is usually drug-refractory, although response to sodium-channel blockers has been described [2].

Gardella et al. [2] reported nine (40.9%) patients with *SCN8A* mutation with tonic-clonic seizures preceded by cyanosis and autonomic features. Our patient presented with a brief breath-holding spell (with perioral cyanosis) followed by behavioral-arrest, and then generalized tonic-clonic seizures. These events were consistently triggered by "breath-holding" before oxcarbazepine. The sequence of provoked crying, breath-holding, bluish discoloration of lips followed by behavioral arrest, and then tonic-clonic limb movements, in a developmentally normal child, was mistaken as isolated breath holding spells with possible reflex-anoxic-seizures. However, video-EEG monitoring proved these events were generalized epileptic seizures following breath-holding spells and prompted the search for a cause.

Yamamoto [3] described three developmentally-normal infants with normal neuro-imaging with generalized tonic-clonic seizures induced by crying who were thought to have "breath-holding spells." Inter-ictal EEG showed frontal spike-waves and ictal-onset was generalized. No

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genetic testing was reported and they responded to valproic-acid. These cases could have been "benign" infantile epilepsy with possible genetic etiology, similar to our case.

Another consideration was that the crying was an ictal phenomenon. The EEG during this phase, only showed diffuse delta-theta slowing which may be secondary to hyperventilation associated with crying. No ictal-EEG patterns were seen till the onset of tonic posturing. Ictal crying has been described in focal epilepsy with poor localizing value.

Hyperventilation may provoke focal seizures, especially temporal lobe seizures [4]. This may explain the episodes of crying triggering the seizures, given the left temporal lesion. Further, the brief behavioral arrest may suggest temporal origin but the EEG was non-localizing. Therefore, it is unclear whether these seizures were reflex seizures triggered by crying or hyperventilation associated with crying provoked them in the setting of a temporal lesion.

Ictal symmetric tonic posturing followed by post-ictal generalized suppression was another notable feature. This has been reported as a possible EEG marker for Sudden-Unexpected-Death-in-Patients-with-Epilepsy (SUDEP).

MRI brain in SCN8A related epilepsy is usually non-specific and may show atrophy. Gardella et al reported no epileptogenic lesion in 22 cases of SCN8A epilepsy [2]. The presence of the left anterior temporal lesion, suspicious for focal cortical dysplasia (concordant inter-ictal EEG, PET, MEG) was unique in our case. Focal cortical dysplasias have been described with other genetic epilepsies (i.e. NPRL3, DEPDC5, LGI1 SLC35A2).

Overall, this report further expands the spectrum of epilepsy phenotypes associated with SCN8A mutations. Crying as a trigger for the seizures, seizures mimicking "breath holding spells" and the presence of a temporal lesion were unique to this case.

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None for any author.

Ethics

Informed consent was taken for the publication of this case report with video.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2019.01.020.

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