Epileptic Disord 2018; 20 (6): 530-4

Intractable apnoeic seizures in a child with a deletion typically associated with Williams syndrome

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Received May 04, 2018; Accepted October 04, 2018

ABSTRACT – Williams-Beuren syndrome is rarely associated with epilepsy. One previously reported case showed an association with apnoeic seizures while a few other cases showed an association with infantile epileptic spasms and generalized and focal seizures. We report the case of a 13-month-old boy with a deletion typically associated with Williams-Beuren syndrome, who presented with isolated apnoeic seizures which were refractory to multiple antiepileptic drugs but partially responsive to the ketogenic diet. The diagnosis was challenging due to a complex cardiac history, gastroesophageal reflux, and normal interictal EEG findings. This case highlights the importance of prolonged EEG monitoring in suspected cases of apnoeic seizures. Further, given the reported cases of unexplained sudden death in Williams-Beuren syndrome, this case raises the possibility of an association between apnoeic seizures and unexplained sudden death. [*Published with video sequence on www.epilepticdisorders.com*]

Key words: apnoea, epilepsy, cyanosis, SUDEP, Brief Resolved Unexplained Event

VIDEO ONLINE

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Isolated apnoeic seizures are a rare and serious condition that can mimic a brief resolved unexplained event (BRUE), formally known as an apparent life-threatening event (ALTE). A BRUE is a sudden, brief, and resolved event that includes at least one of the following:
– cyanosis or pallor;
– absent, decreased or irregular breathing;
– hypo or hypertonia;
– or an altered level of responsiveness (Tieder *et al*., 2016).

Multiple aetiologies can mimic a BRUE, including cardiac, infectious, neurological, gastrointestinal, or metabolic causes. The diagnosis of isolated ictal apnoea is always challenging and requires a high index of suspicion. Prolonged electroencephalogram (EEG) monitoring

doi:10.1684/epd.2018.1013

is occasionally warranted as select cases can have normal interictal EEG findings (Hosain *et al*., 2003).

Williams-Beuren syndrome (WBS), also known as Williams syndrome (OMIM 194050), is a multi-system genetic syndrome caused by a 1.5 to 1.8-Mb hemizygous deletion on chromosome 7q11.23, which affects 28 genes, including one encoding for the protein elastin. The estimated incidence of WBS is 1 in 10,000 live births (Genetics, 2001). WBS has variable clinical manifestations including distinct facial features (*e.g*. elfin face), dental anomalies, systemic arterial stenosis (*e.g*. supravalvular aortic stenosis and pulmonary and renal artery stenosis), hypertension, short stature, hypercalcaemia, gastroesophageal reflux, developmental and cognitive impairment, and a characteristic social personality. Seizures are a rare presentation in WBS, however, there are isolated case reports of infantile epileptic spasms, generalized or focal epilepsy, and ictal apnoea (Tsao and Westman, 1997; Mizugishi *et al*., 1998; Morimoto *et al*., 2003; Tercero *et al*., 2005; Rothlisberger *et al*., 2010; Myers *et al*., 2013; Popp *et al*., 2016; Nicita *et al*., 2016; Samanta, 2017). We report the case of a 13-month-old boy with WBS who presented with intractable apnoeic seizures resistant to multiple antiepileptic drugs. To our knowledge, this is only the second reported case of ictal apnoea in a child with WBS.

Case study

This 13-month-old boy was born via uncomplicated vaginal delivery after an unremarkable pregnancy. Shortly after delivery, he required non-invasive ventilation due to cyanosis and increased breathing. He was subsequently diagnosed with a right-sided pneumothorax which required chest tube insertion. A heart murmur prompted an echocardiogram which showed pulmonary artery stenosis and narrowing of the supravalvular aortic arch. At five months of age, he underwent surgical correction with supra-aortic patch plasty and bilateral pulmonary artery plasty. Due to his characteristic cardiac findings, rapid fluorescence *in situ* hybridization (FISH) was performed and confirmed suspected WBS. Follow-up genomic microarray was diagnostic for Williams syndrome after identifying a 1.711-Mb deletion in chromosome region 7q11.23. His parents are Caucasian and non-consanguineous, and the family history was not contributory. Developmentally, the patient had mild motor and language delay.

At 13 months of age, the patient was admitted to the Hospital for Sick Children due to recurrent apnoeic episodes. During these episodes, he became cyanotic and unresponsive for 30 to 60 seconds and remained lethargic for five minutes. During hospital admission, the episodes were associated with tachycardia, oxygen desaturation, and apnoea. On examination, he had typical WBS facial features, including a broad face and a flattened nasal bridge. Other than generalized hypotonia, his neurological examination was unremarkable.

The patient underwent a detailed cardiac work-up including electrocardiogram (ECG), 24-hour Holter monitor, echocardiogram, and computer tomography (CT) of the chest. No arrhythmia was identified, while the echocardiogram showed a moderately hypoplastic aortic arch, hypoplastic right pulmonary artery, and normal biventricular function. Chest CT identified peripheral pulmonary artery stenosis with diffuse narrowing of the right pulmonary artery. The patient had a history of gastroesophageal reflux that was adequately controlled with anti-reflux medications. Brain MRI at 13 months of age was unremarkable while brain MR angiography showed marked tortuosity of bilateral vertebral arteries, causing mild flattening of the ventral aspect of the medulla. A routine awake EEG was normal and did not capture any clinical events. Prolonged EEG monitoring for 87 hours captured three clinical events which all correlated with apnoeic seizures. Two of the three seizures originated from the right temporal lobe and the third originated from bilateral temporal lobes. There were no interictal epileptiform discharges (*for further details of the seizure events, refer to supplementary figure and the video sequence*).

The patient was initially started on carbamazepine which was discontinued after the first dose due to an allergic skin reaction. He was tested for HLA-A*31:01 and HLA-B*15:02, which were both negative. Clobazam, levetiracetam, and lamotrigine were all trialled without adequate seizure control. Subsequently, a classic ketogenic diet was initiated due to refractory seizures. Repeat brain MRI at two years of age remained normal. Currently, he is two years old with mild to moderate developmental delay and partial control of seizures on classic ketogenic diet, levetiracetam, and lamotrigine.

Discussion

We describe the second reported case of a child with WBS who presented with ictal apnoea. Evaluation of a child with apnoea or cyanotic spells requires careful evaluation and work-up of multiple systems, particularly cardiac, respiratory, gastrointestinal, and neurological. In the previously described case, the diagnosis was challenging given the presence of gastroesophageal reflux along with a complex cardiac history which potentially accounts for the apnoeic

events. Moreover, the absence of other types of clinical seizures and unremarkable initial neurological investigations, including brain MRI and routine EEG, delayed the diagnosis.

The seizures were focal in onset (right temporal lobe) and refractory to three different classes of antiepileptic medications, including benzodiazepine (clobazam), a sodium channel blocker (lamotrigine), and levetiracetam. The ketogenic diet was initiated with partial control of seizures. In the previous case report of WBS with ictal apnoea, abnormal interictal findings on the initial EEG raised clinical suspicion of possible seizures and expedited prolonged EEG (Myers *et al*., 2013), and the apnoeic seizures were controlled on one antiepileptic drug (carbamazepine). However, in our case, the child had an allergic skin reaction to carbamazepine and the seizures were refractory to multiple medications. Of note, levetiracetam was ineffective in both cases.

The pathophysiology of apnoeic seizures is not well understood. Respiration is generated by the respiratory centre in the rostral ventrolateral part of the medulla (Barnes *et al*., 2007) with input from the insular cortex, hypothalamus, and reticular formation. Such connections can be interrupted by generalized or partial seizures arising or spreading to these areas, which can result in respiratory dysfunction (Blum, 2009). Temporal lobe epilepsy with primary focal seizure or secondary generalization has been associated with ictal apnoea in one case series (Bateman *et al*., 2008). Another case series showed that the risk of refractory apnoeic seizures and respiratory dysfunction is increased with spreading of the temporal lobe seizure to the other hemisphere (Seyal and Bateman, 2009).

Our patient with multi-drug resistant epilepsy carried the typical deletion of 1.711 Mb on chromosome 7q11.23. Other than chromosomal microarray, further genomic evaluation was not conducted. These findings support the conclusion from the largest case series of eight patients with epilepsy and WBS that there exists a lack of association between typical or atypical deletion in WBS and seizures, including type or severity (Nicita *et al*., 2016). The case series was conducted after several case reports hypothesized that atypical deletion in WBS, which does not involve *HIP1*, *YWHAG* or *MAGI2* genes, is associated with infantile spasms, epilepsy, and intractable seizures (Mizugishi *et al*., 1998; Marshall *et al*., 2008; Fusco *et al*., 2014). Interestingly, in one case report of a child with WBS due to the typical deletion who had severe epileptic encephalopathy, tri-exome sequencing revealed a *de novo* variant in *GABRA1* (Popp *et al*., 2016). A comparison with our case is limited due to a lack of genomic testing.

Several other studies have shown that the risk of sudden death in WBS is increased with an estimated incidence of 1 in 1,000 patient years (Wessel *et al*., 2004). Although the pathophysiology of sudden death is poorly understood, death is often attributed to cardiac abnormalities (Bird *et al*., 1996). Moreover, multiple studies have shown that ictal hypoventilation may predispose to sudden unexpected death in epilepsy or SUDEP (So *et al*., 2000; Bateman *et al*., 2010; Schuele *et al*., 2011; Jin *et al*., 2017). Our case highlights that a potentially unrecognized cause of sudden death in WBS may be undiagnosed isolated apnoeic seizures. Despite the difficulty finding causal evidence to support this hypothesis, it remains an important possible explanation given the ability to potentially prevent death with adequate seizure control. More importantly, given the frequency of missing isolated ictal apnoeas on routine EEG (Hosain *et al*., 2003), our case highlights the important diagnostic role of prolonged EEG monitoring in select cases with a high index of suspicion. □

Legend for video sequence

At 13 months of age, video-EEG monitoring was performed for five days using 19 scalp electrodes with Oz reference, EMG over the bilateral deltoid muscles, a respiratory monitor, ECG, O_2 saturation, and pulse rate monitor. Three habitual seizures were captured on the fifth day of video-EEG monitoring. The first seizure occurred at 9:42 pm during REM sleep, the second seizure at 03:43 am during wakefulness, and the third seizure at 5:43 am during non-REM sleep. The duration of these seizures ranged from approximately 1 minute to 1.5 minutes, although the offset of ictal EEG change was unclear due to movement/muscle artefacts.

Ictal EEG onset showed a mixture of 15-Hz beta waves and 5-8-Hz spikes over the right fronto-temporal region at Fp2-F4 and F8-T4, followed by rhythmic 3-3.5-Hz spike and waves over the right fronto-temporal region at Fp2-F4, F8-T4, and T6. These activities spread to the right hemisphere as 2-3-Hz delta waves, followed by a build-up of rhythmic 4-5-Hz theta waves over the bilateral temporal regions.

Clinically, the patient presented with apnoea first, which was detected by the respiratory monitor. This was followed by gradual decline of O_2 saturation (down to 21% in the first seizure, 49% in the second seizure, and 52% in the third seizure) and gradual increase in heart rate (up to 144 beats per minute in the first seizure, 166 in the second seizure, and 157 in the third seizure). Towards the end of these seizures, the patient started coughing. During the apnoea, he was moving randomly and did not cry.

In the first seizure, at 21:42:42, a mixture of low-amplitude 15-Hz beta waves and 5-8-Hz spikes started over the right fronto-temporal region at Fp2-F4 and F8-T4. O_2 saturation was 99%, and heart rate was 104 beats per minute (bpm).
At 21:42:55, rhythmic 3-3.5-Hz spike-and-waves were seen over the right fronto-temporal region at Fp2-F4, F8-T4, T6 and C4. O_2 saturation was 95%. Heart rate was 97 bpm.
At 21:42:57, the respiratory monitor detected low amplitude.
At 21:43:00, the patient was aroused from REM sleep and started moving randomly.
At 21:43:07, rhythmic 2-3-Hz delta waves spread to the right hemisphere. O_2 saturation was 93%. Heart rate was 102 bpm.
At 21:43:12, the respiratory monitor showed a flat line.
At 21:43:16, rhythmic 4-Hz theta waves were seen over the right hemisphere. O_2 saturation was 87%. Heart rate was 126 bpm.
At 21:43:23, rhythmic 4-5-Hz theta waves gradually increased with amplitude over the bilateral temporal regions. O_2 saturation was 84%. Heart rate was 129 bpm.
At 21:43:30, the monitor alarm for O_2 saturation sounded. O_2 saturation was 80%. Heart rate was 131 bpm.
At 21:43:52, a mixture of 2-Hz delta waves and 4-5-Hz theta waves spread diffusely. O_2 saturation was 35%. Heart rate was 136 bpm.
At 21:43:53, the pushbutton was activated by his mother.
At 21:43:57, O_2 saturation went down to 21%. Heart rate was 138 bpm.
At 21:44:05, the patient started coughing.
At 21:44:20, O_2 saturation gradually recovered to 58%.

Key words for video research on www.epilepticdisorders.com

Phenomenology: apnoea, desaturation
Localization: right fronto-temporal region
Syndrome: Williams
Aetiology: genetic

Supplementary data.
Summary didactic slides and supplementary figure are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.
We thank the family for providing consent to describe the case with video-EEG data.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What is a brief resolved unexplained event (BRUE) or apparent life-threatening event (ALTE)?

(2) What is the deletion typically associated with Williams syndrome?

(3) What investigations should be ordered in cases of unexplained apnoea in a child with Williams syndrome?

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".