



Intractable apneic seizure in a child with typical deletion of Williams Syndrome

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Intractable apneic seizure in a child with typical deletion of Williams Syndrome

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Abstract:

Williams-Beuren syndrome is rarely associated with epilepsy. One reported case showed an association with apneic seizure and few other cases showed an association with infantile spasms, generalized, and focal seizures. We report the case of a 13-month-old boy with typical deletion of Williams-Beuren syndrome who presented with isolated apneic seizures that were refractory to multiple anti-epileptic drugs and partial response to ketogenic diet. The diagnosis was challenging due to cardiac history, gastroesophageal reflux, and normal inter-ictal electroencephalogram findings. This case highlights the importance of prolonged electroencephalogram monitoring in suspected cases with apneic seizures. Moreover, unexplained sudden death is reported in Williams-Beuren syndrome, and this case raises a possibility of an association between apneic seizures and unexplained sudden death in Williams-Beuren syndrome.

Introduction:

Isolated apneic seizure is a very rare and serious condition that can mimic brief resolved unexplained event (BRUE) or formally known as apparent life threatening event (ALTE) in infancy. The definition of BRUE includes at least one of the following criteria: (1) cyanosis or pallor, (2) absent, decrease or irregular breathing, (3) hypo or hypertonia, or (4) altered level of responsiveness (Tieder et al., 2016). Multiple etiologies can underlie BRUE like symptoms, including cardiac, infectious, neurological, gastrointestinal, or metabolic causes. The diagnosis of isolated ictal apnea is always challenging and requires high clinical suspicion. Prolonged EEG monitoring is sometimes warranted as some cases have normal inter-ictal EEG result (Hosain et al., 2003).

Williams-Beuren syndrome (WBS), also known as Williams syndrome (OMIM 194050), is a multi-systemic genetic syndrome caused by 1.5 to 1.8 Mb hemizygous deletion on chromosome 7q11.23, which includes elastin gene, ELN and other 27 genes. The incidence is estimated to be 1 in 10,000 live births (Genetics, 2001). WBS has variable clinical manifestations including certain facial features (e.g. elfin face), dental anomalies, systemic arterial stenosis (e.g. supraaortic stenosis, pulmonary and renal artery stenosis), hypertension, short stature, hypercalcemia, gastrointestinal abnormalities, developmental and cognitive impairment, and characteristic social personality. Seizures are a rare presentation in WBS; however, there have been a few published case reports of infantile spasms, generalized or focal epilepsy, and ictal apnea (Myers et al., 2013, Mizugishi et al., 1998, Morimoto et al., 2003, Tsao and Westman, 1997, Samanta, 2017, Rothlisberger et al., 2010, Tercero et al., 2005, Popp et al., 2016, Nicita et al., 2016). We are reporting a 13-month-old boy with WBS who presented with intractable apneic seizures resistant to multiple anti-epileptic drugs. To our knowledge, this is the second reported case of ictal apnea in a child with WBS.

Case summary:

This is a 13 months old boy born via uncomplicated vaginal delivery at term after normal pregnancy. Shortly after delivery, he required non-invasive ventilation due to cyanosis and increase work of breathing. He was diagnosed with right pneumothorax and chest tube was inserted. Due to a heart murmur, he had echocardiogram completed which showed right pulmonary artery stenosis and narrowing of the supravulvar aortic arch.

At five months, he underwent supra-aortic patch plasty and bilateral pulmonary artery plasties to repair the supravulvar aortic stenosis and bilateral pulmonary artery stenosis.

Due to the cardiac findings, fluorescence in situ hybridization (FISH) was sent and confirmed the diagnosis of Williams Syndrome. A follow up genomic microarray showed 1.711 Mb deletion in chromosome region 7q11.23 which is diagnostic for Williams syndrome. He had mild motor and language delay. His parents were non-consanguineous and the family history was not contributory.

At age of 13 months, he was admitted to the Hospital for Sick Children due to recurrent apneic episodes. During these episodes, he became cyanotic and unresponsive for 30 to 60 seconds and remained lethargic for five minutes. During hospital admission, these episodes were associated with tachycardia, oxygen desaturation, and apnea. On initial examination, he had mild dysmorphic features including broad face and flattening of nasal bridge. He had generalized hypotonia. His neurology exam was otherwise unremarkable.

He had full cardiac investigations including electrocardiogram (ECG), 24-hour Holter monitor, echocardiogram, and CT chest. There was no arrhythmia identified on Holter monitor. Echocardiogram showed moderately hypo-plastic aortic arch, hypo-plastic right pulmonary artery, and normal biventricular function. CT chest showed peripheral pulmonary artery stenosis with diffuse narrowing of right pulmonary artery. He had a

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3 history of gastroesophageal reflux that was controlled with anti-reflux medications.
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5 Brain MRI was unremarkable. Brain MR angiography showed marked tortuosity of
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7 bilateral vertebral arteries, causing mild flattening of ventral aspect of medulla. A routine
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9 awake EEG was normal, although it did not capture any clinical events. A prolonged
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11 EEG monitoring for 87 hours captured three clinical events which all correlated with
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13 apneic seizures. Two of the three seizures originated from the right temporal lobe and the
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15 third originated from bilateral temporal lobes. There were no inter-ictal epileptiform
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17 discharges. The seizure events are described in detail in the supplementary data section.
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19 Initially, he was started on carbamazepine which was discontinued after the first dose
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21 due to an allergic skin reaction. He tried clobazam, levetiracetam, and lamotrigine
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23 without adequate seizure control. He was subsequently started on classic ketogenic diet
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25 due to refractor epilepsy to multiple anti-epileptic drugs. Currently, he is two years old,
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27 on classic ketogenic diet, levetiracetam, and lamotrigine with partial control of seizures,
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29 and mild to moderate developmental delay.
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Discussion:

We describe the second reported case of a child with WBS who presented with ictal apnea. The diagnosis was challenging given the history of gastroesophageal reflux and complex cardiac history of supraventricular aortic stenosis and pulmonary arteries stenosis that could have explained the apnea. Moreover, the absence of other types of clinical seizure and unremarkable initial neurological investigations including brain MRI and routine EEG played a role in delaying the diagnosis. The seizures were focal in onset (right temporal lobe) and, unfortunately, refractory to three different classes of anti-epileptic drugs, including benzodiazepine (clobazam), sodium channel blocker (lamotrigine), and levetiracetam. Ketogenic diet was started with partial control of seizures. In the previous case report of WBS with ictal apnea, abnormal inter-ictal findings on the initial EEG raised a suspicion of seizures and expedited prolonged EEG (Myers et al., 2013). Further, apneic seizures were controlled on one anti-epileptic drug (carbamazepine). However, in our case, the child had an allergic skin reaction to carbamazepine and his seizures were refractory to multiple medications. Both cases failed a trial of levetiracetam for seizure control.

The pathophysiology of apneic seizures are not well understood. Respirations are generated by the respiratory center in rostral ventrolateral part of medulla (Barnes et al., 2007). Insular cortex, hypothalamus, and reticular formation provide input to the medullary respiratory center. Such connection can be interrupted by generalized or partial seizures arising or spreading to these areas, which can lead to respiratory dysfunction (Blum, 2009). Temporal lobe epilepsy with primary focal seizure or secondary generalization has been associated with ictal apnea in a case series study (Bateman et al., 2008). Another case series showed the risk of refractory apneic seizures

and respiratory dysfunction will be increased with spreading of temporal lobe seizure to the other hemisphere (Seyal and Bateman, 2009).

Our case suffered from multi-drug resistant epilepsy and carried the typical deletion of 1.711 Mb on chromosome 7q11.23; however, a genomic study was not conducted. Such finding supports the conclusion of the largest case series of 8 patients with epilepsy and WBS, which concluded a lack of association between typical or atypical deletion in WBS and seizure or its severity (Nicita et al., 2016). That study was conducted after several case reports hypothesized that atypical deletion in WBS, which does not involve HIP1, YWHAG or MAGI2 genes are 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 child with WBS due to typical deletion associated with severe epileptic encephalopathy, a tri-exome sequencing revealed a de novo variant in GABRA1(Popp et al., 2016). A comparison to our case is limited due to lack of genomic test.

Several studies have demonstrated that the risk of sudden death in WBS is increased with an estimated incidence of 1/1,000 patient years (Wessel et al., 2004). Although the pathophysiology of sudden death is poorly understood, it is often attributed to cardiac abnormalities (Bird et al., 1996). Moreover, multiple studies showed that ictal hypoventilation may predispose to sudden unexpected death in epilepsy (SUDEP)(Bateman et al., 2010, Jin et al., 2017, So et al., 2000, Schuele et al., 2011).

This case highlights that a potentially unrecognized cause of sudden death in WBS cases may be undiagnosed isolated apneic 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. Also, given the

easily missed diagnosis of isolated ictal apnea in a routine EEG (Hosain et al., 2003), this case highlights the importance role of prolonged EEG monitoring in diagnosis.

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Ethical Approval: Written informed consent was obtained from the patient's guardian for publication of this case report.

Key learning questions:

1) What does brief resolved unexplained event (BRUE) or apparent life threatening event (ALTE) in infancy means?

The definition of BRUE includes at least one of the following criteria: (1) cyanosis or pallor, (2) absent, decrease or irregular breathing, (3) hypo or hypertonia, (4) altered level of responsiveness.

2) What is the typical deletion in Williams Syndrome?

There will be hemizygous deletion of 1.5 to 1.8 Mb on chromosome 7q11.23, which contains approximately 28 genes.

3) What to order in case of unexplained apnea in a child with Williams Syndrome despite the initial work up?

Prolonged video EEG to capture these events.

Video EEG legend:

At 13 months of age, video-EEG monitoring was performed for 5 days using 19 scalp electrodes with Oz reference, EMG over the bilateral deltoid muscles, respiratory monitor, ECG, O2 saturation and pulse rate monitor. Three habitual seizures were captured on the 5th day of the video-EEG monitoring. The first seizure occurred at 9:42pm during REM sleep, the second seizure at 03:43am during wakefulness, and the third seizure at 5:43am during non-REM sleep. The duration of these seizures approximately ranged from 1 minute to 1.5 minute although the offset of ictal EEG change was unclear due to the movement/muscle artifacts. 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 apnea first, which was detected by the respiratory monitor. This was followed by gradual decline of O2 saturation (down to 21% in the first seizure; 49% in the second seizure; 52% in the third seizure), and gradual increase of heart rate (up to 144 beats per minute in the first seizure; 166 in the second seizure; 157 in the third seizure). Toward the end of these seizures, the patient started coughing. During the apnea, he was moving randomly and did not cry.

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3 In the first seizure, at 21:42:42, a mixture of low amplitude 15 Hz beta waves
4 and 5-8 Hz spikes started over the right fronto-temporal region at Fp2-F4 and
5 F8-T4. O2 saturation was 99%, and heart rate 104 beats per minute (bpm).
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11 At 21:42:55, rhythmic 3-3.5 Hz spike-and-waves were seen over the right
12 fronto-temporal region at Fp2-F4, F8-T4, T6 and C4. O2 saturation 95%. Heart
13 rate 97 bpm.
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18 At 21:42:57, respiratory monitor became low amplitude.
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22 At 21:43:00, the patient was aroused from REM sleep and started moving
23 randomly.
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28 At 21:43:07, rhythmic 2-3 Hz delta waves spread to the right hemisphere. O2
29 saturation 93%. Heart rate 102 bpm.
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34 At 21:43:12, respiratory monitor showed flat line.
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39 At 21:43:16, rhythmic 4 Hz theta waves were seen over the right hemisphere.
40 O2 saturation 87%. Heart rate 126 bpm.
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45 At 21:43:23, rhythmic 4-5 Hz theta waves gradually increased the amplitude
46 over the bilateral temporal regions. O2 saturation 84%. Heart rate 129 bpm.
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51 At 21:43:30, the alarm of O2 saturation monitor went off. O2 saturation 80%.
52 Heart rate 131 bpm.
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At 21:43:52, a mixture of 2 Hz delta waves and 4-5 Hz theta waves spread diffusely. O2 saturation 35%. Heart rate 136 bpm.

At 21:43:53, the pushbutton was activated by his mother.

At 21:43:57, O2 saturation went down to 21%. Heart rate was 138 bpm.

At 21:44:05, the patient started coughing.

At 21:44:20, O2 saturation was gradually recovering to 58%.

Key words for video EEG:

Syndrome: Williams

Aetiology: genetic

Phenomenology: apnea, desaturation

Localization: right fronto-temporal region

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