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The Burst Suppression Pattern in 4-Year-Old with SNAP 25 Mutation: A Case Study

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Abstract

Burst suppression is an EEG (electroencephalograph) pattern that can be observed when patients are under the influence of general anesthetics, in severe conditions such as cerebral anoxia, or rare epileptic encephalopathies, like Ohtahara syndrome, which manifest in the neonatal period. We present a child with a de-novo mutation of SNAP25 and a burst suppression pattern that persisted after the neonatal period. The patient has a history of seizures and a global developmental delay since infancy. Her EEG in the neonatal period demonstrated hypsarrythmia and burst suppression, and the burst suppression pattern continues to be present at four years of age. We suggest that the SNAP25 mutation of the patient is the likely cause of the burst suppression EEG pattern.

Keywords: SNAP25; Burst Suppression; Ohtahara Syndrome; EEG; Epilepsy

Introduction

Burst suppression is a distinct electroencephalographic (EEG) pattern which is comprises two elements: 1) high amplitude bursts pattern (which can be single/grouped/ polyspikes mixed with delta-theta activity) and 2) a depressing background or inactivity, which lasts for a longer duration than the bursts. These two patterns come in an alternating fashion and make up the typical burst suppression pattern [1]. [1] Burst suppression can be seen in various conditions, such as the use of general anesthetics, sedative overdoses, cerebral anoxia (caused by cardiorespiratory arrest), and rare epileptic encephalopathies [1]. In cases of severe epileptic encephalopathies, the burst suppression pattern can appear in the neonatal period and is known as early infantile epileptic encephalopathy with suppression-burst, or Ohtahara syndrome [2]. In Ohtahara syndrome, burst suppression classically evolves into hypsarrythmia at 3-6 months of age, and is known as West Syndrome if present with epileptic spasms and neurodevelopmental regression. [3] This pattern can further develop into the synchronous slow spike and wave discharges at around 1-3 years of age, which are the hallmarks of the Lennox-Gestuat syndrome [3]. We report a patient with a de novo SNAP25 mutation who continues to demonstrate the burst suppression pattern on EEG at the age of 4. The genes involved in fetal brain development are heavily linked with seizure disorders, and mutations in almost half of them can result in epilepsy [4]. One such gene is associated with SNAP25 protein. SNAP 25 is a component of the SNARE (soluble N-ethylmaleimide-sensitive factor attachment receptor) complex, which is involved in the transport of synaptic vesicles and controls intracellular calcium levels [5]. Mutations in SNAP25 are suggested to be a new genetic cause of epilepsy and intellectual disability, as reported by a few case studies [6-10].

Case Presentation

A 4-year-old female with a history of epileptic encephalopathy and West Syndrome presented to the emergency department for further evaluation of new apneic episodes. The patient had been well until four days before the presentation when she started developing thick secretions. Upon admission, she was observed to have an episode of eye blinking, tongue thrusting, and rhythmic facial twitching along with several episodes of apnea.

The patient was put on video EEG monitoring which was notable for continuous spike and wave discharges at 1.5-2hz suggestive of ongoing ictal activity (figure 1a). The clinical seizure and the ictal EEG pattern was aborted with intravenous Lorazepam (figure 1b). Following the resolution of status epilepticus, EEG showed a diffuse slow pattern and alternating burst suppression pattern during sleep (figure 1d). The pattern persisted after the patient was seizure-free and at her baseline functionality.

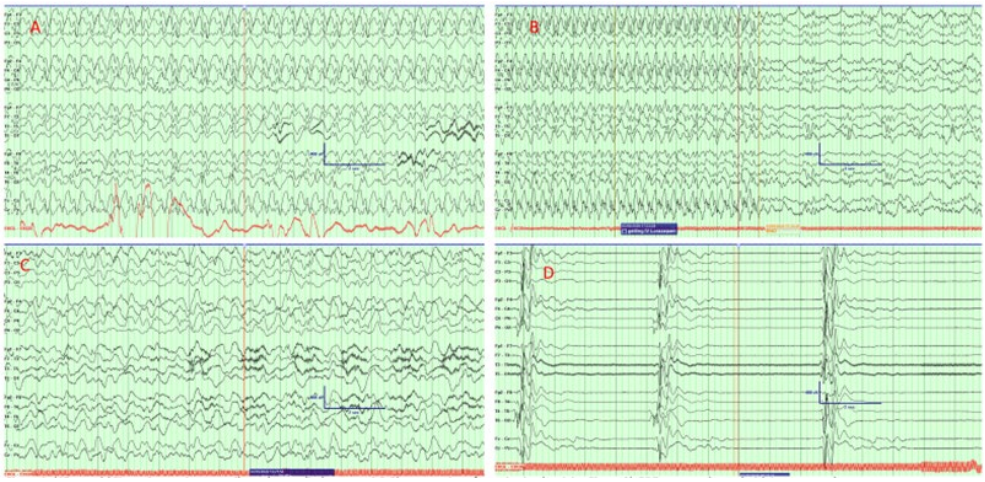

Figure 1: (47 months) Figure 1a continuous spike and wave discharges at 1.5-2 Hz suggestive of ongoing ictal activity. (Figure 1b) EEG pattern aborted with intravenous lorazepam, (Figure 1c) diffuse slow pattern alternating with (Figure 1d) burst suppression pattern in sleep. Sensitivity 10uV/mm. Time base 15mm/sec for all except 1b which has 25mm/sec. Bipolar montage left above right.

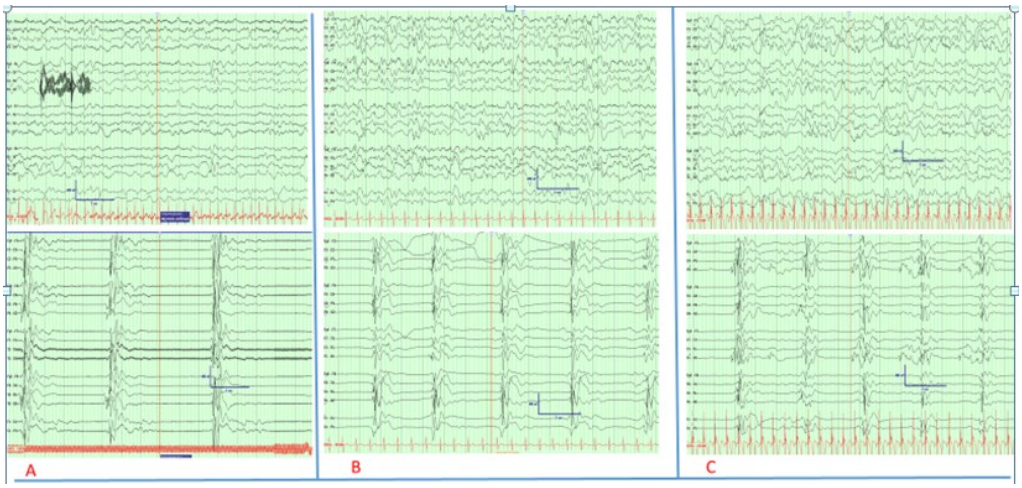

Figure 2: Serial EEG showing showed diffuse slowing while awake (top) and burst suppression pattern in sleep (bottom) (Figure 2a) 8 months, (Figure 2b) 19 months, (Figure 2c) 31 months pattern while asleep Sensitivity 10uV/mm. Time base 15mm/sec, Bipolar montage left above right.

The patient was born full-term via C-section. She had her first seizure when she was two months of age. She had global developmental delay and was later diagnosed with West Syndrome. Family history is remarkable for Autism

Spectrum Disorder in her brother, but no family history of seizure disorder.

On examination, the patient does not maintain eye contact or obey commands. She has poor verbal skills. She has decreased tone in her axial muscles and increased tone of the extremities. She is currently maintained on multiple antiepileptic medications including the ketogenic diet, valproic acid, levetiracetam, phenobarbital, vigabatrin, and cannabidiol.

Previous metabolic workup was unremarkable, including a normal acylcarnitine profile, free/total carnitine, plasma amino acids, urine organic acids, and blood creatine/guanidinoacetate level. Genetic testing was significant for a mutation of **the Gln174Ter variant (Variant of Uncertain Significance) of SNAP 25 gene c.520 C>T** found in the epilepsy genetic panel and confirmed on the whole-exome sequencing. Neuroimaging showed diffuse white matter loss.

Past EEG records showed diffuse slowing while awake and the burst suppression pattern while asleep at the ages of 8, 19, and 31 months. These are shown in figures 2a, 2b, and 2c, respectively.

Discussion

Burst suppression is a typical EEG pattern and can be seen in a deeper stage of general anesthesia, sedative overdoses and/or cardiorespiratory arrest [1] it can also be observed in rare neonatal epileptic encephalopathies such as Ohtahara syndrome [2]. Ohtahara syndrome typically evolves into West Syndrome, which consists of the triad of epileptic spasm, neurodevelopmental regression, and hypsarrythmia on EEG [3] West Syndrome classically transforms into the Lennox-Gastaut Syndrome [3].

Our patient continues to have a burst suppression pattern at age 4. The finding of this pattern is usually associated with a poor prognosis. There are a few reported findings that link the burst suppression pattern with seizure activity, for example, the blood-brain barrier breaks during burst suppression as well as during a seizure [11]. This correlation remains controversial, as burst suppression can also be induced by many antiepileptic drugs, like anesthetics. Burst suppression has been reported before during sleep in a patient with the history of accidental brain anoxia following neuromuscular blocker injection, who recovered his functionality even though the EEG pattern of burst suppression persisted [12].

Index	Gender Age at Diagnosis	SNAP25 Mutation	Seizure Type (Present at any life Stage)	EEG findings
1 [10]	Male 1 year 6 months	c.496G>T, p.Asp166Tyr	Generalized tonic-clonic seizures, focal seizures	Generalized spike wave, continuous spike and wave during sleep
2 [6]	Female 5 months	c.142G>T, p.Val48Phe	Generalized tonic-clonic seizures, focal seizures	Mild generalized slowing, interictal partial and symptomatic generalized discharges, and ictal partial and generalized seizures
3 [9]	Female Early childhood	c.200T>A p.Ile67Asn	Intermittent eyelid ptosis, blank stare, unresponsiveness	Generalized atypical poly-spike and wave discharges and diffuse slowing of the background rhythm
4 [8]	Female 1 year 5 months	c.176G>C, p.Arg59Pro	Generalized tonic-clonic seizures, focal seizures, myoclonic seizures, drop attacks	Normal
5 [8]	Male 1 year 1 month	c.176G>C, p.Arg59Pro	Generalized tonic-clonic seizures, focal seizures, complex partial seizures	Frontocentral discharges with focal spike-wave
6 [8]	Male Not Described	c.118A>G, p.Lys40Glu	Absence seizures	Not Described
7 [7]	Female Not Described	c.127G>C, p.Gly43Arg	Generalized tonic-clonic seizures	Not Described
8*	Female Infant	c.520C>T, p.Gln174Ter	Clusters of flexion spasms	Burst suppression pattern with generalized high amplitude slow spike and wave discharges, hypsarrhythmia

*The same patient is in this paper.

Table 1: Comparison of patients with SNAP25 mutations and epilepsy.

In our case, the persistence of the burst suppression pattern may be attributed to several possible etiologies, including the severity of the patient's seizures and the administration of sedative medications. These are unlikely causes, however, as the burst suppression pattern persisted after both adequate seizure control and the weaning of her sedative medications. We propose that this unique finding is due to the specific pathways related to the patient's known SNAP25 mutation, as epilepsy can be caused by genetic or acquired factors. Genetic causes make up 32% of the cases of childhood-onset epilepsies, [13] and are composed of genes that belong to ion-channel or non-ion-channel protei [4]. One such protein is SNAP25.

SNAP25 is found in the presynaptic and postsynaptic membranes and the plasma membrane of the neuroendocrine cells [5]. It is involved in the vesicular release and regulation of Ca^{2+} via the associated channel [5]. SNAP25 has two splice variants; SNAP25a and SNAP25b [14]. It has been found that mutations resulting in the elimination of SNAP25b expression, causing SNAP25a to be the only expressed variant, produce developmental defects and spontaneous seizures in the mouse model. [14] Recent genetic studies on humans [6-10] report that SNAP25 is a possible cause of different neurological diseases such as epilepsy.

A de novo mutation was detected in our patient's SNAP25 gene c.520 C>T Q174X (Glutamine > Unknown). According to reports, other mutations of SNAP25 may be the cause of epilepsy and intellectual disabilities, such as c.496G>T, [10] c.142G>T, [6] c.200T>A, [9] c.176G>C, [8] c.118A>G, [7] and c.127G>C [7] (Table 1). It has also been reported that de novo mutations in SNAP25 are statistically significantly related to neurodevelopmental disorders with epilepsy. [7]

None of the reported SNAP25 mutation cases with epilepsy had burst suppression findings on EEG. (Table 1) This finding demonstrates the diverse level of symptoms that can be associated with the SNAP25 mutation.

Conclusion

We recommend testing for rare DNA mutations, especially SNAP25, when the burst suppression pattern is observed in children with epilepsy and who are of atypical age. The persistence of burst suppression even after the seizure control is of unknown significance and likely depicts the unique mutation found in this patient or the severity of the patient's condition. Under similar cases, more extensive research work is required to reach any conclusion. As this event is a rare phenomenon, a case-controlled study might be indicated in the future to determine if there is any significant relationship between this genotype and the diverse phenotypes that are seen in patients affected by this mutation.

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