CASE REPORT

Electrical Status Epilepticus during Sleep in a Male Filipino with Rare Nonsense Mutation Variant of Sotos Syndrome on Carbamazepine Monotherapy

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ABSTRACT

Electrical status epilepticus during sleep (ESES) is an electrographic pattern associated with specific genetic disorders, brain malformations, and use of some antiseizure medications. This case report aims to present the management of ESES in Sotos syndrome (SoS) on carbamazepine.

A nine-year-old Filipino male with clinical features suggestive of overgrowth syndrome presented with febrile seizure at one year old. Cranial imaging showed cavum septum pellucidum, corpus callosal dysgenesis, and ventriculomegaly. He was on carbamazepine monotherapy starting at three years old. A near continuous diffuse spike–wave discharges in slow wave sleep was recorded at nine years old hence shifted to valproic acid. Follow-up study showed focal epileptiform discharges during sleep with disappearance of ESES. Next generation sequencing tested positive for rare nonsense mutation of nuclear receptor binding set-domain protein 1 confirming the diagnosis of SoS.

Advanced molecular genetics contributed to determination of ESES etiologies. To date, this is the first documented case of SoS developing ESES. Whether an inherent genetic predisposition or drug-induced, we recommend the avoidance of carbamazepine and use of valproic acid as first-line therapy.

Keywords: Sotos syndrome, electrical status epilepticus during sleep, carbamazepine

Poster presented at the 15th Asian Oceanian Congress of Child Neurology (AOCCN), September 19-22, 2019, Kuala Lumpur, Malaysia and at the 13th Asia Pacific Conference on Human Genetics, November 7-9, 2019, Manila, Philippines; 1st Place, Electronic Poster Presentation at the 40th Annual Convention Philippine Neurological Association, November 13-16, 2019, Manila, Philippines.

eISSN 2094-9278 (Online)
Published: March 15, 2024
https://doi.org/10.47895/amp.vi0.3013

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INTRODUCTION

With the advent of molecular genetics, the use of appropriate antiseizure medications (ASMs) tailored for specific gene-related epilepsy and epilepsy syndromes become more and more accessible to practicing neurologists. This also led to avoidance of certain ASMs that have been documented to exacerbate seizure or produce drug-related side effects to certain diseases and genetic syndromes. One example of this precision medicine is among individuals with pathogenic mutation in sodium voltage-gated channel alpha subunit 1 (SCN1A) gene seen in more than 80% of patients with Dravet syndrome. Strong evidence against the use of sodium channel blockers have improved its current management of epilepsy.[1]

Unlike certain epilepsy and epilepsy syndromes, attempts to determine a single definite etiology of electrical status epilepticus during sleep (ESES) remain elusive in the past decades as its estimated prevalence (0.5%) among those with epilepsy is relatively low. Also, no genetic or non-genetic causations can satisfactorily fulfill the clinical phenotypes and neuropsychologic profile of patients, especially in

children. ESES, as defined by the International League Against Epilepsy (ILAE) is the occurrence of significant activation or near continuous epileptiform discharges during sleep (Commission on Classification and Terminology of the ILAE 1989).[2] No rigid diagnostic criteria as to the cut-off value of spike-wave index have been established at present.

This report presents the management of Sotos syndrome (SoS) with a rare mutation variant in a 9-year-old Filipino male on carbamazepine monotherapy who developed ESES. Furthermore, it explores SoS genetic predisposition to develop ESES and propose a primary ASM of choice among those with epilepsy.

CASE PRESENTATION

We report a 9-year-old male, born preterm (32 weeks) to a non-consanguineous Filipino descent. He had infantile laryngomalacia, early-onset abnormal rapid growth particularly macrocephaly, delayed motor and cognitive milestones, and dysmorphic features such as prominent forehead, sparse hair on the frontoparietal region, low nasal bridge, malar hypoplasia, and long palm. He had global developmental delay before five years old and intellectual disability with attention deficit and hyperactivity disorder beyond five years old. His clinical phenotype, developmental, neuropsychological features, and neuroimaging findings (Figure 1) were suggestive of a childhood overgrowth syndrome (Table 1), presumptive of SoS. Both parents are non-dysmorphic and have average height for age and sex. There were no other family members with the same phenotypic characteristics and had seizure or epilepsy.

He had onset of febrile focal-impaired awareness seizure (FIAS) at one year old followed by an unprovoked (afebrile) tonic-clonic seizure before two years old. Phenobarbital (5 mg/kg/day) was started. His first routine electroencephalography (EEG) showed inter-ictal generalized epileptiform discharges. After six months on phenobarbital, he manifested hyperactive behavior prompting shift to carbamazepine (10 mg/kg/day). After more than two years of reported seizure freedom, a repeat routine EEG at five years old showed very frequent bilateral frontal epileptiform discharges hence carbamazepine was continued. At seven years old, myoclonic seizures were reported and repeat routine EEG showed the presence of ESES (Figure 2).

He was managed as ESES. Carbamazepine was shifted to valproic acid (VPA) at 20 mg/kg/day. There was a >50% reduction of myoclonic seizure with no dose-related side effects. VPA was then increased to 30 mg/kg/day with reported improvement of hyperactive behavior and clinical seizure freedom. A video-EEG after nine months of VPA monotherapy showed occasional left occipital and right temporal epileptiform discharges during Stage II of sleep, with disappearance of ESES. The patient's seizure semiology in relation to age of onset, EEG findings, and antiseizure medications used in comparison to reported natural history of seizures in SoS is shown in Figure 3.

Table 1. Patient's Summary of Dysmorphic Features and Onset of Clinical Presentation

Age	Clinical Presentation and Pertinent Diagnostic Work-up
Birth – <6 months	• Birthweight: large for gestational age (>95P for gestational age) Normal head circumference at birth (50P for gestational age) but with rapid head circumference growth starting at 3 months (>95P for age) Laryngomalacia Decreased visual acuity *Cranial Ultrasound: Cavum septum pellucidum, ventriculomegaly*
6 months – 1 year	• Normalization of head circumference Febrile seizure Global developmental delay (GDD): gross & fine motor, and speech delay *Auditory brainstem evoked response: normal*
1 – 5 years	• Unprovoked (afebrile) seizure Dysmorphic features: prominent forehead, sparse hair on the frontoparietal region, low nasal bridge, malar hypoplasia, long palm Accommodative esotropia *Normal thyroid function* *Male karyotype (46, XY)* *Fragile X screening negative* *Normal whole abdominal ultrasound* *Cranial CT scan: Frontal lobe atrophy, ex vacuo dilatation of the ventricles, and cavum septumpellucidum*
5 years – present	• Intellectual disability Attention deficit/hyperactivity disorder *Vineland adaptive behavior scale: adequate daily living skills (personal, domestic and community) but moderately low communication (receptive, expressive, and written), socialization (interpersonal, play and leisure, and coping) and motor (gross and fine) skills* *Cranial MRI: cavum septumpellucidum, corpus callosal dysgenesis, and ventriculomegaly (Figure 1); Chest CT scan: Normal* *Invitae Overgrowth and Macrocephaly Syndromes Panel: (+) NSD1, variant at exon 20 of chromosome 5 (6013C>T), heterozygous.*

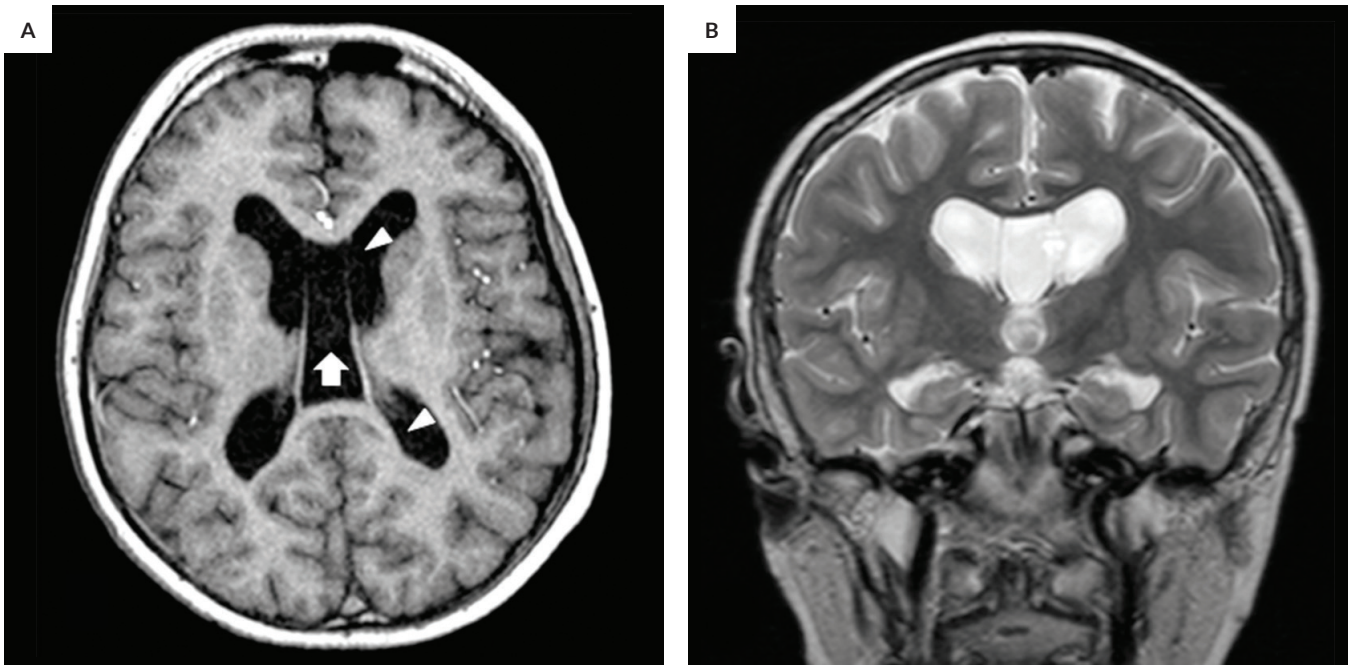

Figure 1. ***Cranial MRI of patient.*** **(A)** Axial T1 weighted image showing cavum septum pellucidum *(arrow)* ventriculomegaly with prominent trigone and occipital horns *(arrow head)*, corpus callosal dysgenesis, and **(B)** coronal T2 fluid attenuated inversion recovery-weighted images showing normal hippocampus and absence of heterotopia.

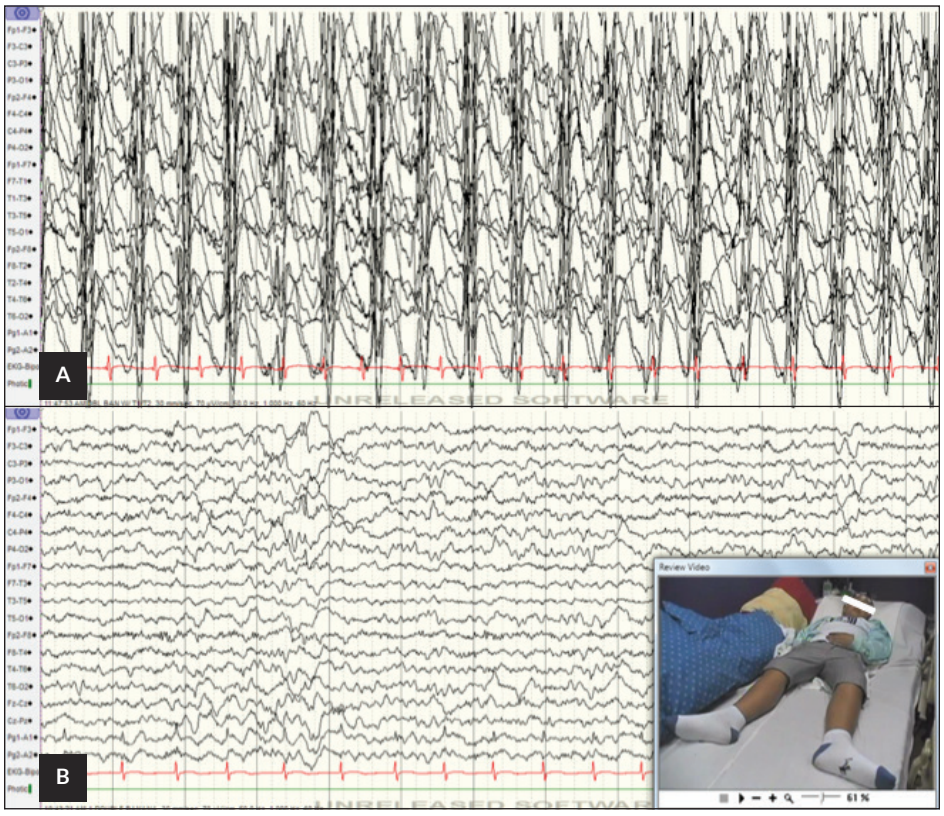

Figure 2. A 21-channel digital electroencephalography showing an almost continuous runs of **(A)** generalized high voltage polyspikes and **(B)** slow wave complexes that were not associated with clinical events during sleep.

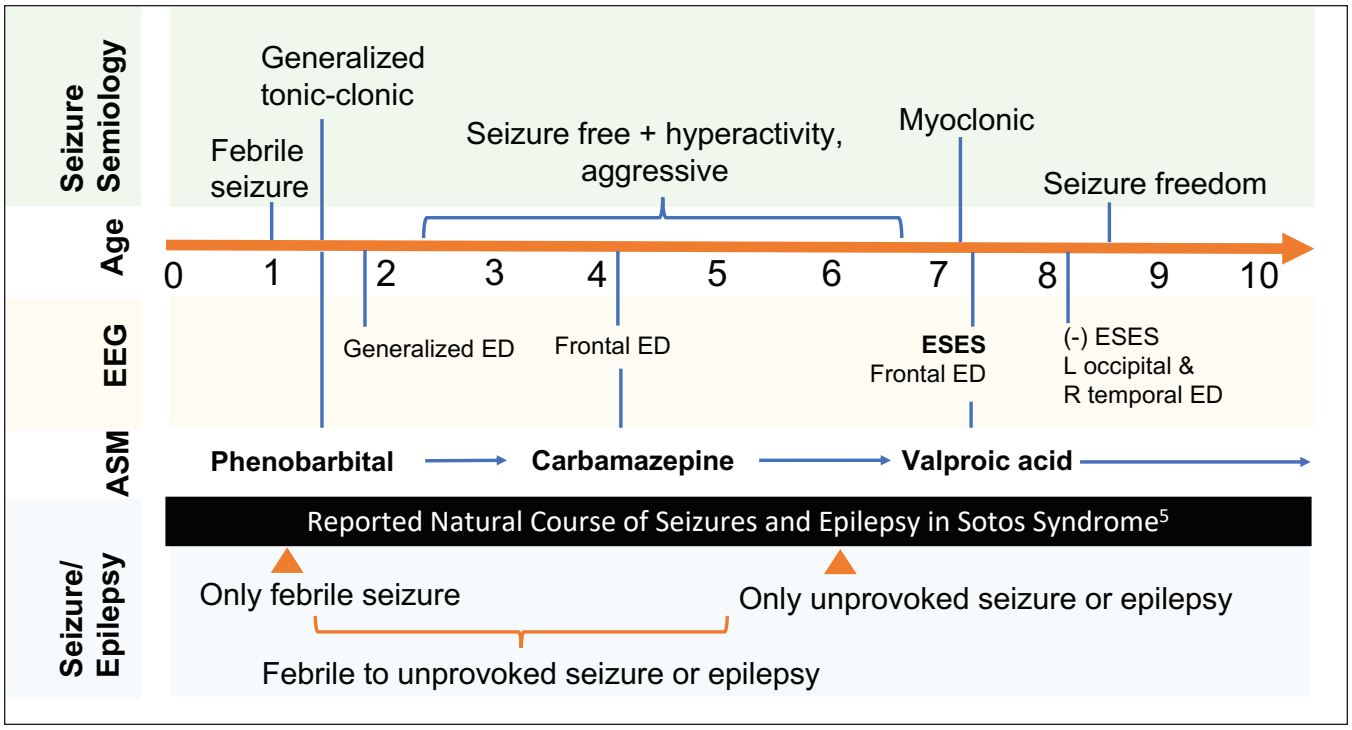

Figure 3. Schematic diagram of patient's seizure evolution, electrographic pattern, and initiation or timing of antiseizure medications with correlation to reported natural courses of seizures and epilepsy in SoS.

ASM – antiseizure medication, ED – epileptiform discharge

To determine the possible genetic association of ESES to childhood overgrowth syndrome and determine clinical implications to management and prognosis, a next generation sequence was done which revealed positive for a rare pathogenic variant coding for nuclear receptor binding SET domain protein 1 (NSD1) confirming the diagnosis of SoS.

DISCUSSION

SoS is one of the clinically overlapping overgrowth syndrome characterized by three cardinal features of typical facial dysmorphisms, learning disability, and overgrowth in height and/or head circumference. It is an autosomal dominant syndrome due to haploinsufficiency of NSD1 located at chomosome 5q35 in 90% reported individuals.[3] NSD1 encodes for histone methyltransferase implicated in cell growth and differentiation particularly chromatin regulation and transciption repression or activation.[4] Our patient's genetic testing revealed a rare nonsense mutation variant at exon 20 (6013C>T) that creates a premature translational stop signal. Both parents of our patient were not similarly affected which suggests the possibility of de novo mutation. At present, no exact frequency in gene-based population databases is available for this specific type of mutation variant but four reported cases showed probable increased propensity for learning disability, overgrowth, and/or sacrococcygeal teratoma.[4]

An estimated 9-50% of SoS develop febrile seizure and epilepsy such as infantile spasms, absence, tonic–clonic, and myoclonic seizures. There are no SoS-associated brain malformations that increases the risk for epilepsy except for three reported cases of heterotopias.[5,6] In addition, prominent behavioral and emotional disturbances were observed among SoS compared to individuals with non-syndromic epilepsy.[7]

ESES is a rare age-related epilepsy syndrome characterized by a constellation of different seizure types, neuropsychological impairment, and typical electrographic findings.[2] The exact etiology remains uncertain. A systematic review by Kessi et al. have recognized that among patients with ESES and other closely related electrographic pattern such as epilepsy-aphasia spectrum and continuous spike-wave of slow sleep, approximately 37% (56/151) solely linked pathogenic genes for encoding channels in the brain neurons. These findings however, may not be sufficient since few cytogenetic studies had been made among these ESES patients prior to the era of molecular studies.[1]

Paradoxically, ASMs have been shown to aggravate seizure either clinically or electrographically resulting in evolution of ESES. Carbamazepine, phenytoin, phenobarbital, and oxcarbazepine were documented to induce ESES, typically presents with unexplained regression and stagnation of development.[7,8] The exact mechanism of drug-induced ESES is largely unknown but some proposed the involvement of

channelopathy pathway as these drugs mostly act on specific ion channels in the nervous system.[9]

Clinical and electrographic resolution of ESES had been shown with conventional ASMs particularly high-dose benzodiazepines and valproic acid. Other relatively newer ASMs such as levetiracetam and lacosamide also showed response but robust data is needed. Steroid is an acceptable option for those who do not respond to benzodiazepines and with likely immunologic etiology of ESES.[7,10,11] Valproic acid was the drug of choice for our patient since it has an added mood stabilizing effect. Its mechanism can be attributed to normalization of circadian rhythm due to elevated dopamine levels.[12,13]

CONCLUSION

SoS is associated with seizures and epilepsies. With an increased preponderance to behavioral and emotional disturbances, it is vital to determine an appropriate antiseizure medication that offers good seizure control and avoid exacerbation of co-morbidities. This is the first case of SoS with a rare pathogenic variant in NSD1, developing ESES while on carbamazepine monotherapy. It is known that ESES may clinically manifest with behavioral and cognitive disturbances which could potentially aggravate SoS. We therefore recommend the avoidance of carbamazepine among those SoS with epilepsy. VPA can be an alternative first line antiseizure medication with added mood stabilizing effect.

Statement of Authorship

All authors contributed in the conceptualization of work, acquisition of data and analysis, drafting and revising of manuscript, and approved the final version submitted.

Author Disclosure

All authors declared no conflicts of interest. The corresponding author secured the consent from the parent of the patient for the publication of the report.

Funding Source

The study was funded by the authors.

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