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SHORT RESEARCH ARTICLE

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Seizures in Sotos syndrome: Phenotyping in 49 patients

Olivier Fortin[1] | **Christian Vincelette**[2] | **Afsheen Q. Khan**[3] | **Saoussen Berrahmoune**[3] | **Christelle Dassi**[3] | **Mitra Karimi**[3] | **Ingrid E. Scheffer**[4,5,6] | **Jun Lu**[7] | **Kellie Davis**[8] | **Kenneth A. Myers**[1,3,9]

[1]Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, Quebec, Canada

[2]School of Nursing, Faculty of Medicine and Health Sciences, University of Sherbrooke, Sherbrooke, Quebec, Canada

[3]Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

[4]Epilepsy Research Centre, Department of Medicine, Austin Health, The University of Melbourne, Heidelberg, Victoria, Australia

[5]Department of Paediatrics, Royal Children's Hospital, The University of Melbourne, Flemington, Victoria, Australia

[6]The Florey Institute of Neuroscience and Mental Health, Heidelberg, Victoria, Australia

[7]Department of Pediatrics, Haikou People's Hospital, Haikou, China

[8]Division of Medical Genetics, Department of Pediatrics, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

[9]Department of Neurology & Neurosurgery, Montreal Children's Hospital, McGill University, Montreal, Quebec, Canada

Correspondence
Kenneth A. Myers; Montreal Children's Hospital; MUHC Glen Site; 1001 Décarie Blvd; Montreal, Quebec H4A 3J1; Canada.
Email: kenneth.myers@mcgill.ca

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Abstract

We aimed to describe the phenotypic spectrum of seizures in Sotos syndrome, a genetic condition involving overgrowth, macrocephaly, dysmorphic features, and learning disability, in which 60%-90% have *NSD1* pathogenic variants. Patients were recruited from clinics and referral from support groups. Those with seizures and a clinical diagnosis of Sotos syndrome were included. Phenotyping data were collected via structured clinical interview and chart review. Forty-nine patients were included. Twenty had *NSD1* testing results available; of these, 15 (75%) had *NSD1* pathogenic variants. Seizure onset age ranged from 3 months to 12 years. Staring spells (absence or focal impaired awareness seizure) were the most frequently reported semiology (33/49; 67%), followed by febrile seizures (25/49; 51%) and afebrile bilateral tonic-clonic seizures (25/49; 51%). Most patients (33/49; 67%) had multiple seizure types. The majority (33/49; 67%) had seizures controlled on a single antiseizure medication or no medication. Nine (18%) had drug-resistant epilepsy. Epilepsy syndromes included febrile seizures plus, Lennox-Gastaut syndrome, childhood absence epilepsy, and generalized tonic-clonic seizures alone. The seizure phenotype in Sotos syndrome most commonly involves staring spells, afebrile tonic-clonic seizures or febrile convulsions; however, other seizure types may occur. Seizures are typically well-controlled with medication, but drug-resistant epilepsy occurs in a minority.

KEYWORDS

febrile seizures, febrile seizures plus, NSD1, Sotos syndrome

1 | BACKGROUND

Sotos syndrome (OMIM 117550), first described in 1964,[1] is characterized by the cardinal triad: characteristic facial features (dolichocephaly, frontal bossing, hypertelorism, high-arched palate, prominent jaw), childhood overgrowth (including macrocephaly), and learning disability.[2] The estimated incidence is 1 in ~15 000 newborns.[2] Heterozygous pathogenic variants in *NSD1* (OMIM 606681), encoding nuclear receptor-binding set domain protein 1, are found in 60%–90% of patients.[2-4] However, there is genetic heterogeneity, with pathogenic variants in *NFIX* (OMIM 164005) and *APC2* (OMIM 612034) also associated with Sotos-like phenotypes.[5,6]

Approximately half of Sotos syndrome patients have seizures, with half of those exhibiting febrile convulsions only.[7] The prevalence of afebrile seizures in S0000000000000000000otos syndrome is variable in the literature,[2,7] and there are few data regarding the phenotypic spectrum of seizure presentations.[8] This study evaluated a cohort of Sotos syndrome patients with seizures, in order to describe the clinical, genetic, radiologic, and neurophysiologic features.

2 | METHODS

Patients with Sotos syndrome and a history of seizures were identified through review of the authors' respective clinical and research databases, and by patient self-referral following liaison with the Sotos Syndrome Support Association. The Sotos syndrome clinical diagnosis was determined based on published clinical criteria[9] or a medical note confirming the clinical diagnosis had been made by a geneticist. We also considered a known pathogenic variant in *NSD1* as sufficient for diagnosis.[10] Data were collected using clinical interviews conducted in person or by telephone, and medical charts were reviewed when available. Written informed consent was obtained from patients or caregivers. The study was approved by the local research ethics board.

3 | RESULTS

Forty-nine patients (26 males) with Sotos syndrome and seizures were included, drawn from eight different countries (United States, Canada, Australia, United Kingdom, Ireland, Honduras, Singapore, and Germany). Five patients were directly evaluated in clinic by one of the authors. The remaining 44 patients were identified through self-referral through the Sotos Syndrome Support Association, and a telephone interview was conducted by one of the authors for all of these patients. Age at evaluation ranged from 14 months to 49 years. Age at Sotos syndrome diagnosis was from the neonatal period to age 13 years. Two were published previously.[11,12]

3.1 | Sotos syndrome clinical features

Most patients (47/49; 96%) had craniofacial dysmorphisms although two patients were described as "mild" and three as "slightly atypical." Forty-five patients had overgrowth (92%), and 47 had macrocephaly (96%); 48 patients (98%) had one or the other. Forty-eight patients (98%) had variable degrees of developmental or learning difficulties, with data unavailable for one patient.

3.2 | Seizure types

Five patients (10%) had febrile seizures only, and 44 patients (90%) were considered to have a clear diagnosis of epilepsy (Table 1). Age at seizure onset was between 3 months and 12 years (mean 4.5 years). The most frequently reported

TABLE 1 Clinical features of 49 patients with Sotos syndrome and seizures

Clinical features	Percentages (n)
Seizure types	
Staring spells	67% (33)
Febrile seizures	51% (25)
Afebrile bilateral tonic-clonic seizures	51% (25)
Myoclonic seizures	22% (11)
Atonic seizures	21% (10)
Hypermotor seizures	8% (4)
Epileptic spasms	6% (3)
Tonic seizures	8% (4)
Epilepsy syndromes	
Febrile seizures plus	40% (19)
Lennox-Gastaut syndrome	8% (4)
Childhood absence epilepsy	4% (2)
Epilepsy with generalized tonic-clonic seizures alone	4% (2)
Epilepsy with myoclonic absences	2% (1)
Sleep-related hypermotor epilepsy	2% (1)
West syndrome	2% (1)
Myoclonic-atonic epilepsy	2% (1)
EEG findings	
Normal	20% (9)
Interictal abnormalities	61% (21)
Epileptiform abnormalities	20% (9)
Diffuse slowing	6% (3)
Unspecified anomalies	16% (8)
Seizures	24% (12)
Report unavailable	20% (9)

seizure type was "staring spells," observed in 33 patients (67%). Although the review of the clinical semiology and medical notes, when available, was convincing for an ictal event, it was often difficult to differentiate a clear absence seizure from a focal impaired awareness seizure based on history alone. Febrile seizures (n = 25; 51%) and afebrile bilateral tonic-clonic seizures (n = 25; 51%) were also frequently reported. Other reported seizure types included myoclonic (n = 11; 22%), atonic (n = 10; 21%), hypermotor (n = 4; 8%), epileptic spasms (n = 3; 6%), and tonic seizures (n = 4, 8%). Thirty-three patients (67%) had multiple seizure types. With regard to specific epilepsy syndromes, 19 patients (40%) had febrile seizures plus (FS+), four had Lennox-Gastaut syndrome (LGS), two had childhood absence epilepsy (CAE; childhood-onset typical absence seizures with 3-Hz generalized spike-wave on EEG), two had epilepsy with generalized tonic-clonic seizures alone, one had epilepsy with myoclonic absences, one had sleep-related hypermotor epilepsy, one had West syndrome, and one had myoclonic-atonic epilepsy (MAE). For the remaining patients, a clear diagnosis of an epilepsy syndrome was difficult to establish based on the available clinical data.

3.3 | Seizure treatment

Nine patients (19%) had never received an antiseizure medication (ASM) at the time of the clinical interview, in most cases because they had only febrile seizures. Seventeen patients (34%) achieved adequate control of seizures on a single ASM, and seven (14%) were now seizure-free after weaning off medication. Six patients (12%) needed two ASMs for adequate control, and one patient had responded to two ASMs in combination with the ketogenic diet. Nine patients (18% of the overall cohort, 20% of those with epilepsy) had drug-resistant epilepsy, one of whom also had vagus nerve stimulator implantation.

3.4 | EEG

Forty-six patients (94%) had had an EEG at some point in the course of their disease. Of these, the EEG was normal in nine (20%) and abnormal in 28 (61%), with results not available in the remaining nine (20%). Of the 28 patients with abnormal EEGs, nine had interictal epileptiform abnormalities (focal in 1, multifocal in 1, generalized in 4, and not more precisely specified in 4), three had diffuse slowing and eight had unspecified anomalies. Twelve patients had seizures captured on EEG (absences in 3, atonic in 2, and unclear semiology in the remaining 7). Four patients had LGS based on clinical features and EEG characteristics.

3.5 | Neuroimaging

Forty-six patients had a brain MRI, 21 of whom had abnormalities on imaging, including ventriculomegaly (17), enlarged extraaxial spaces (5), corpus callosum dysgenesis (7), and white matter signal changes (4).

3.6 | Genetic testing

Twenty patients had available genetic information that included *NSD1* evaluation (Table 2); of these, 15 (75%) had a pathogenic variant. Three patients had deletions affecting *NSD1*, five had variants predicted to result in premature protein truncation, one had an intronic variant predicted to affect splicing, and five had missense variants. One patient had a complex chromosomal rearrangement leading to partial deletion of *NSD1*. For 15 more patients, parents reported that their child had a positive genetic test for Sotos syndrome, but we were unable to obtain the genetic testing results with the specific *NSD1* mutation. The parents of two patients were confident that no genetic testing had been done. For the remaining 12 patients, caregivers were unsure if *NSD1* sequencing had been performed. The clinical phenotype based on the specific *NSD1* pathogenic variant is given in Table 2. For the three patients with whole-gene deletions, we were not able to identify a consistent epilepsy phenotype. Similarly, for the 12 patients with confirmed *NSD1* point mutations—all of whom had different variants—we were not able to correlate a cluster of mutation for a specific epilepsy phenotype.

4 | DISCUSSION

The data from this large Sotos syndrome cohort shed important light on the range of possible seizure presentations which can occur in this genetic syndrome. "Staring spells" were the most frequent reported seizure type, though these likely included both true generalized absence seizures and focal impaired awareness seizures (FIAS); differentiating the two was challenging as we did not have EEG data from all patients and often had to rely on clinical history alone. The next most common seizure semiologies were febrile and afebrile bilateral tonic-clonic seizures. The majority of patients had multiple seizure types, with most patients who initially presented with febrile seizures later developing afebrile seizure types as well. Among the patients that had febrile seizures only, 4 were relatively young at the time of clinical interview (18 months, 3 years, 5 years, and 6 years, respectively) and may not have had the time to develop other seizure types; the fifth patient had his first febrile seizure past the age of 6 years and was thus diagnosed with FS+.

TABLE 2 Pathogenic variants identified and associated clinical features

#	Pathogenic variant	Seizure types	Epilepsy syndrome (if applicable)	Response to ASM
1	Chr5q35 deletion	FIAS/Absence	–	Never on ASM
6	*NSD1* c.5141C>G (p.Ser1714*)	FIAS/Absence, FS, GTC	FS+	Controlled with LEV
11	*NSD1* c.5854C>T (p.Arg1952Trp)	FIAS/Absence, eyelid fluttering, myoclonic seizures	–	Controlled with TPM, CLB and KD
13	*NSD1* c.1810C>T (p.Arg604*)	FS only	–	Never on ASM
14	Chromosome 5 rearrangement (Deletion of exons 5 and 6 of *NSD1* and arr[hg18] 5p12p11(45,515,589-46,286,429)x3)	FIAS/Absence	–	Weaned off ASM
16	*NSD1* c.4991G>A (p.Cys1664Tyr)	GTC	Epilepsy with generalized tonic-clonic seizures alone	Controlled on CBZ
18	Chr5q35.3 deletion	FS, GTC	FS+	Controlled on VPA
31	*NSD1* c.6613C>T (p.His2205Tyr)	Absence (confirmed)	CAE	Weaned off ASM
33	*NSD1* c.6061C>T (p.His2021Tyr)	FS only	–	Never on ASM
35	Chr5q35 deletion	FS, GTC, Myoclonic seizures	FS+with myoclonic seizures	Controlled on VPA and CLB
41	*NSD1* c.1644delT (p.Asn549Metfs*6)	FS, GTC	FS+	Controlled on VPA and LTG
42	*NSD1* c.3214C>T (p.Arg1072*)	GTC	Epilepsy with generalized tonic-clonic seizures alone	Never on ASM
46	*NSD1* c.5431dupC (p.Arg1811Profs*9)	FS only	–	Never on ASM
48	*NSD1* c.5509G>A (p.Ala1837Thr) (* also had a rare intronic variant: c.5509 + 2 T > G)	FIAS/Absence, Atonic, Myoclonic, Tonic seizures	LGS	Refractory to multiple ASM (ESM, CZP, BRV, LEV, CLB, LTG, PER)
49	*NSD1* c.3496−1G>A	Absence, GTC, Tonic, NCSE	LGS	Refractory to multiple ASM (ESM, AZM, CBZ, PHT, TPM, LTG, VPA)

Abbreviations: ASM, antiseizure medication; AZM, acetazolamide; BRV, brivaracetam; CAE, childhood absence epilepsy; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; FIAS, focal impaired awareness seizures; FS, febrile seizures; FS+, febrile seizures plus; GTC, generalized tonic-clonic; KD, ketogenic diet; LEV, levetiracetam; LTG, lamotrigine; NCSE, nonconvulsive status epilepticus; PER, perampanel; PHT, phenytoin; TPM, topiramate; VPA, valproic acid.

A diagnosis of an epilepsy syndrome was made in 31 patients; however, this was quite variable, ranging from FS+to more severe phenotypes including LGS and West syndrome. Based on EEG data, patients may have features of either generalized, focal, or multifocal epilepsy. The course of seizures tends to be relatively benign and self-limited. Most patients were seizure-free either untreated or on a single AED; however, a minority of patients had drug-resistant epilepsy. Despite not having genetic data for every patient, we are still able to report specific clinical phenotypes for some of the pathogenic variants reported in this study; this genotype-phenotype correlation, although limited given the number of cases, could be useful for clinicians caring for these patients. Unfortunately, we cannot comment more generally on genotype-phenotype correlation, due in part to the small size of the cohort and lack of recurrent variants identified. Furthermore, for the five patients with negative *NSD1* testing and the 14 patients with unclear genetic testing, we were unable to assess whether they had a pathogenic variant in another gene with a Sotos phenotype, such as *NFIX* or *APC2*.

Our data contrast somewhat with what was previously the largest study of seizures in Sotos syndrome, a cohort of 19 patients by Nicita et al[8] As with our cohort, they reported a large proportion of patients with febrile seizures (11/19, 58%) and only a small fraction of patients with drug-resistant epilepsy (1/19, 6.5%). However, they reported a smaller proportion with afebrile tonic-clonic seizures (7/19, 37% versus 51% in our cohort). They reported a combined 32% (6/19) with what were likely staring spells (five with temporal lobe seizures, and one with temporal lobe and absence seizures) compared with 67% in our study. Similar to our results, they found that structural abnormalities such as ventriculomegaly and corpus callosum dysgenesis were often seen on neuroimaging; however, there were no clearly epileptogenic focal lesions.

Our results should be considered with some caution, given the limitations of the study. Most of the clinical data were obtained through phone interviews, and, although these were comprehensive, this retrospective enquiry introduces a risk of recall bias. The telephone-based interview also impaired the specificity of our enquiry with regard to the exact seizure type. We attempted to triangulate data by reviewing patient charts; however, we were unable to obtain complete records for all patients. Additionally, given that the majority of patients were recruited via self-referral, there is the potential for selection bias, possibly skewing our results toward more severely affected individuals.

We also note that Sotos syndrome is a genetically heterogeneous condition, and epilepsy phenotypes may be at least partially dependent on the underlying gene responsible. For example, Mastrangelo et al recently reported a patient with Sotos syndrome due to compound heterozygous *APC2* pathogenic variants, who had epilepsy with eyelid myoclonia; this epilepsy phenotype was not seen in any of our cohort.[13] Biallelic *APC2* pathogenic variants may also result in a non-Sotos phenotype involving lissencephaly and subcortical heterotopia; these patients tended to have generalized tonic-clonic or myoclonic seizures.[14]

Based on our results, clinicians and families can be reassured that when patients with Sotos syndrome develop seizures, the course is usually uncomplicated, and seizures are often self-limited. However, some patients do develop drug-resistant epilepsy; further research is needed to evaluate why this occurs and what the best treatments are in those cases.

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CONFLICTS OF INTEREST

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ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Anonymized data will be shared by request from any qualified investigator.

ORCID

Ingrid E. Scheffer https://orcid.org/0000-0002-2311-2174
Kenneth A. Myers https://orcid.org/0000-0001-7831-4593

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