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STXBP1 encephalopathy is associated with awake bruxism

Arezoo Rezazadeh [a], Mohammed Uddin [b], O. Carter Snead III [c], Victor Lira [a], Alexandra Silberberg [d], Shelly Weiss [c], Elizabeth J. Donner [c], Maria Zak [c], Laura Bradbury [c], Stephen W. Scherer [b,e], Alfonso Fasano [f,g], Danielle M. Andrade [a,g,*]

[a] Krembil Neurosciences Epilepsy Genetics Program, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada
[b] The Centre for Applied Genomics, Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Ontario, Canada
[c] Division of Neurology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
[d] Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[e] Department of Molecular Genetics and McLaughlin Centre, University of Toronto, Toronto, Ontario, Canada
[f] Edmond J. Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, Ontario, Canada
[g] Division of Neurology, Department of Medicine, Toronto Western Hospital, Krembil Neuroscience Centre, University of Toronto, Toronto, Ontario, Canada

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ABSTRACT

Heterozygous mutations in syntaxin-binding protein 1 (*STXBP1*) gene are associated with early infantile epileptic encephalopathy 4 (EIEE4). This condition is characterized by epilepsy, developmental delay (DD), and various movement disorders. Herein, we will report 5 unrelated patients with different de novo mutations in *STXBP1*. In addition, we conducted an online survey through Facebook to identify the incidence of bruxism (BRX) in these patients. Four out of 5 patients (80%) presented with awake BRX (A-BRX). Bruxism was also reported in 81.4% (57/70) of the patients with STXBP1 encephalopathy through the online questionnaire. No consistent correlation was identified between the type of mutation and development of movement disorders or BRX. This is the first study to demonstrate A-BRX in patients with *STXBP1* mutation. Given the role of *STXBP1* in exocytosis of neurotransmitters and other manifestations of dopamine dysregulation in patients with *STXBP1*-EIEE4, we suggest that in patients with *STXBP1* encephalopathy, A-BRX might be the result of the involvement of dopaminergic circuits.

1. Introduction

Early infantile epileptic encephalopathy 4 (EIEE4) or Ohtahara syndrome is a severe condition linked to *STXBP1* heterozygous mutations [1]. However, mutations in this gene have also been reported in patients with nonsyndromic intellectual disability or epilepsy [2,3]. Hypotonia, ataxia, spasticity as well as various types of movement disorders such as intention tremor, dyskinesia, dystonia, and parkinsonism have been described in affected patients [4,5]. Herein, we studied the phenotype of patients with STXBP1 encephalopathy, and for the first time, we report awake bruxism (A-BRX) in these patients.

2. Material and methods

Patients were recruited from the adult epilepsy genetics clinic and pediatric epilepsy clinics at Toronto Western Hospital and The Hospital for Sick Children, respectively. All patients were examined by two epileptologists (AR and DA) and one movement disorder specialist (AF).

We also carried out an online survey through an *STXBP1* group on Facebook, inquiring about the presence of "tooth grinding" in these patients. The consent for inclusion in the study was obtained as per research ethics board protocols approved by the University Health Network (UHN).

3. Results

Five patients with pathogenic *STXBP1* variants were identified in the clinics. Four out of these five patients (80%) presented with A-BRX. Bruxism was reported by 57 out of 70 families of patients with STXBP1 encephalopathy who responded to the online questionnaire

Abbreviations: A-BRX, awake bruxism; BRX, bruxism; CNS, central nervous system; DD, developmental delay; DR2, dopamine receptor 2; EIEE4, early infantile epileptic encephalopathy 4; MUNC18-1, mammalian uncoordinated-18-1; *STXBP1*, syntaxin-binding protein 1.

* Corresponding author at: UHN — Toronto Western Hospital, 5W–445, 399 Bathurst St., Toronto, ON M5T 2S8, Canada.
E-mail addresses: arezoo.rezazadeh@one-mail.on.ca (A. Rezazadeh), Mohammed.Uddin@mbru.ac.ae (M. Uddin), carter.snead@sickkids.ca (O.C. Snead), lexi.silberberg@mail.utoronto.ca (A. Silberberg), shelly.weiss@sickkids.ca (S. Weiss), elizabeth.donner@sickkids.ca (E.J. Donner), maria.zak@sickkids.ca (M. Zak), laura.bradbury@sickkids.ca (L. Bradbury), Stephen.Scherer@sickkids.ca (S.W. Scherer), alfonso.fasano@uhn.ca (A. Fasano), Danielle.Andrade@uhn.ca (D.M. Andrade).

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Table 1
Demographic, clinical, genetic, imaging, and electroencephalographic findings of patients with STXBP1 mutation.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
STXBP1 pathogenic variation	c.1702 + 1 G > A	c.875G > A	c.755 T > C	Intragenic deletion included exon 2–13	c.1061G > A,
Protein	−	p.Arg292His	p.Meth262Thr	−	p.Cys354Tyr
Other genetic/genomic findings	−	VUS in SPRED—c.1313G > T, (p.Gly438Val); a benign variant in GLI2—c.4558G > A (pAsp1520Asn).	−	CNV dup in 11p15.1	−
Gender, age at inclusion (y)	M, 33	M, 45	M, 7	M, 11	F, 46
Development prior to seizure onset/age at onset of stagnation or regression	NA	Delayed	Normal	Normal	Delayed
Degree of ID	Severe	Severe	Moderate	Severe	Severe
Seizure onset age	One day	3 days	13 months	4 months	8 years
Seizure type at onset	Myoclonic and tonic seizures	GTCS	GTCS	Infantile spasms	Head drop and nonresponsiveness
Current seizure types	FIAS, epileptic spasm, tonic seizure, gelastic seizure	GTCS, staring episodes	Nocturnal epileptic spasm, GTCS (1–2/y)	Staring spells, FIAS, GTCS, and myoclonic jerking	GTCS
Presence of dyskinesia/stereotypies	Choreoathetoid movements, focal dystonia in the right leg, cluster of startles	Stereotyped trunk movements	−	Chorea	−
Bruxism	−	+	+	+	+
Parkinsonism	−	No-no head tremor; trunk dyskinesia; resting and postural low frequency tremor in the arms; cogwheel rigidity at his wrists	−	−	Hypomimia; asymmetric resting tremor involving predominantly the upper limbs, slight cogwheel rigidity at her right wrist; stooped posture
Other neurological abnormalities	Semicontinuous spontaneous and stimuli-induced distal polymyoclonus, hypertonicity	Asymmetric upper and lower limbs spasticity	Diffuse hyporeflexia	Generalized hypotonia, bilateral stimulus-induced myoclonic jerking, and areflexia in his upper limbs. The plantar reflexes were upgoing on the right side and equivocal on the left side.	Action jerky tremor involving predominantly the upper limbs; fluctuating resting tremor in her lower limbs (slow orthostatic tremor); unsteady stance; wide-based and short-step gait
Dysmorphism and other abnormal features	Brachydactily	Short philtrum and a small mouth, strabismus, thoracic kyphosis	−	Right eye exotropia, large ears, small hands, clinodactyly, unilateral flexion contracture in the left wrist, unilateral overriding toes	−
EEG at onset	Slow background with asymmetrical intermittent epileptic activity	Bilateral independent ictal activity (right > left)	Normal	Hypsarrhythmia	NA
EEG at follow-up	Multifocal epileptiform disturbance at 1 year	Right postcentral IED at 2.5 years	(Evidence of) epileptic spasm localized to the left hemisphere at 3 years and MISF at 3.5 years	Diffuse voltage attenuation with superimposed beta waves with posterior head prominence at 2–3 months	NA
Last EEG	Electrodecremental pattern with overriding low amplitude fast ictal beta activity not lateralizing/localizing at 24 years	Fast activities in the frontal regions at 3.5 years	Epileptiform discharges over the right hemisphere 5 years	MISF in addition to intermittent attenuation of the background at 27 months	Bisynchronous interictal epileptiform discharges in the bifrontal head regions as well as MISF at 30 years
MRI images	Mild generalized cerebral atrophy at 20 years	Minimally dilated Sylvian fissures and convolutional sulci in brain CT 2 months	Nonspecific focal signal abnormality in the medial aspect of the right frontal lobe in addition to dilated periventricular space, especially in corpus callosum at 2 years	Generalized prominence of the extra-axial CSF spaces, and the myelination appeared to be lagging particularly in the frontal lobes at 2 years	Mild diffuse atrophy at 31 years
Additional comments	Paternal family history of dystonia	−	Visual evoked potential (at 2 months) showed delayed cortical response	Responded to a 12-month course of ketogenic diet	−

CNV: copy number variant; CT: computed tomography; dup: duplication; EEG: electroencephalography; F: female; FIAS: focal impaired awareness seizure; GTCS: generalized tonic–clonic seizure; ID: intellectual disability; IED: interictal epileptiform discharges; M: male; MISF: multiple independent spike foci; MRI: magnetic resonance imaging; NA: not available; VUS: variant of uncertain significance; y: year.

(81.4%). Among these patients, 79.3% had A-BRX, and 19% were reported to have both awake and asleep BRX.

The other clinical features, demographics, genetic results, neuroimaging, and electroencephalographs (EEGs) of the 5 patients seen in the clinic are described in Table 1. All 5 patients were born to healthy nonconsanguineous parents. The median age at time of inclusion was 33 years. Four were male, and one was female. Three had normal early development prior to the seizure onset. Information about early development of one patient was not available. All patients showed severe global developmental delay (DD) at the time of inclusion. The median age of seizure onset was 4 months. Various seizure types were observed including epileptic spasm, tonic seizures, generalized tonic–clonic seizures, focal impaired awareness seizures, gelastic seizures, and myoclonic seizures. All patients had seizures refractory to the antiepileptic medications tried.

Patient 1 presented with significant choreoathetoid movements and focal dystonia in the right leg, requiring botulinum toxin injections. Examination of patient 2 revealed trunk dyskinesias as well as resting and action tremor of both hands (resting tremor is more severe on the right hand). He also presented A-BRX needing botulinum toxin injections (Video 1). Patient 3 did not show dyskinesia, stereotypies, or parkinsonism but had A-BRX. Patient 4 developed episodic involuntary choreic movements at the age of 7 years that gradually aggravated but responded appropriately to the combination of clonazepam and tetrabenazine. He also had A-BRX. Patient 5 also developed parkinsonism shortly after the seizure onset, requiring levodopa. He had A-BRX in the last examination.

The neuroimaging in patients 1, 2, 4, and 5 demonstrated mild cerebral atrophy.

4. Discussion

Most of the clinical manifestations of the patients in this study are very similar to those of other published series of patients with STXBP1 encephalopathy. However, to our knowledge, this study is the first series to report A-BRX in patients with pathogenic *STXBP1* mutations. In our study, A-BRX was observed in 80% of patients seen in the clinic, and it was reported in 79.3% of patients with STXBP1 encephalopathy identified through an online survey.

Although some authors suggest that BRX is simply a form of stereotypy seen in patients with DD [6], dopamine dysfunction has been implicated as a cause of BRX. For instance, Rett syndrome, a rare X-linked neurodevelopmental disorder, presents with a wide spectrum of hyperkinetic and hypokinetic movement disorders including dystonia, rigidity, and tremor [7]. Similar to our patients, a high percentage of BRX has been reported in patients with Rett syndrome (80%) [7]. Dopamine insufficiency has been implicated in patients with Rett syndrome [8]. Interestingly, when our group examined patients with Lennox-Gastaut syndrome, we did not identify any cases of A-BRX. All of our Lennox-Gastaut patients had severe DD and epilepsy without a clear dopamine deficiency. They were genetically tested and none of them had a pathogenic STXBP1 variant [9].

Syntaxin-binding protein 1 is a member of Sec1 protein family and is crucial for presynaptic vesicle fusion and exocytosis [10]. The link between STXBP1 (also known as mammalian uncoordinated-18-1 (MUNC18-1)) and dopamine metabolism has been demonstrated in animal studies showing that Munc18-interacting (Mint) proteins contribute to induce striatal dopamine release [11]. Hyperkinetic and hypokinetic features such as dyskinesia, dystonia, intention tremor, and parkinsonism, which are frequently reported in patients with STXBP1 encephalopathy, could also be linked to dysregulation of dopaminergic system.

Other studies have shown the role of dopamine receptors in BRX. For instance, the G allele of dopamine receptor D2 (*DRD2*) and the C allele of dopamine receptor D5 (*DRD5*) genes are associated with a significant risk reduction of BRX [12]. It is suggested that carriers of the G allele have an increased density of dopamine receptor 2 (DR2) and higher dopaminergic activity in central nervous system (CNS), leading to a protective effect against BRX [12].

The role of the dopaminergic system in BRX could be seen through drugs that act on dopamine content or dopamine receptors. Short-term use of levodopa can attenuate BRX both in patients with Parkinson disease and healthy subjects [13]. Dopamine receptor 2 agonist such as bromocriptine has been shown to reduce BRX [14]. On the other hand, dopaminoceptor antagonists (specifically DR2 antagonists) are also known to cause BRX [15].

4.1. Limitations

The small number of patients with STXBP1 encephalopathy seen in the clinic might prevent the findings from being extrapolated, although we tried to support our findings through an online questionnaire. The small number of patients with STXBP1 encephalopathy seen in the clinic precluded us from identifying an association between the abnormal movements in this group of patients and BRX. We do not know the exact *STXBP1* mutations of patients who responded to the online questionnaire. Furthermore, there might be a selection bias regarding the patients who responded to the online questionnaire, although the percentage of individuals affected with A-BRX in those 70 families were identical to our patients seen in the clinic. We could not ask about the other abnormal movements of the patients through the online questionnaire as those would have to be verified by a careful neurologic examination. Finally, we did not attempt to treat A-BRX with dopaminergic drugs, since this was not the goal of this study.

5. Conclusion

Bruxism has been shown to cause dental wear, jaw muscle pain, fatigue, and temporal headaches in the affected patients [16]. Here, we described A-BRX in 80% of patients with *STXBP1* mutation, who present commonly with epileptic encephalopathy and movement disorders. Although A-BRX has been categorized as stereotypy by some authors [6], others believe that this is a result of dopaminergic dysfunction. Given the role of *STXBP1* in the striatal dopamine release, we hypothesized that disruption in dopamine metabolism in these patients is linked to the A-BRX. The small size of studied population examined in the clinic is a limitation, but the online questionnaire suggests that A-BRX is not uncommon. Future studies might elucidate the nature and, hopefully, provide better treatment for this distressing manifestation of STXBP1 encephalopathy.

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Author contributions and disclosures

Arezoo Rezazadeh
Contribution: Performed the chart review, analyzed the data, and wrote the manuscript and tables.
'Declarations of interest: none'.

Mohammed Uddin
Contribution: Analyzed the genetic data of the patients in the study.
'Declarations of interest: none'.

O. Carter Snead III
Contribution: Provided the medical data and the genetic data of the patients in the study. Reviewed and edited the manuscript.
'Declarations of interest: none'.

Victor Lira
Contribution: Assisted in chart review and drafting the manuscript.
'Declarations of interest: none'.

Alexandra Silberberg
Contribution: Assisted in chart review and drafting the manuscript.
'Declarations of interest: none'.
Shelly Weiss
Contribution: Provided the medical data and the genetic data of the patients in the study. Reviewed and edited the manuscript.
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Elizabeth J. Donner
Contribution: Provided the medical data and the genetic data of the patients in the study. Reviewed and edited the manuscript.
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Maria Zak
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Laura Bradbury
Contribution: Provided the medical data and the genetic data of the patients in the study.
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Stephen W. Scherer
Contribution: Analyzed the genetic data of the patients in the study.
'Declarations of interest: none'.

Alfonso Fasano
Contribution: Assessed the movement disorders of the patients in the study.
'Declarations of interest: none'.

Danielle M Andrade
Contribution: Developed the research question and designed the study. Reviewed and edited the manuscript.
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