Clinical Case Report

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Therapeutic benefits of ACTH and levetiracetam in STXBP1 encephalopathy with a de novo mutation

A case report and literature review

Shunli Liu, MB[a,b], Liyuan Wang, MM[a,b], Xiao Tang Cai, MD[a,b,*], Hui Zhou, MD[a,b], Dan Yu, MD[a,b], Zhiling Wang, MD[a,b]

Abstract

Rationale: The case report aims to discuss the clinical symptoms and treatment of encephalopathy caused by a novel syntaxin-binding protein 1 (STXBP1) genetic mutation.

Patient concerns: The patient, a girl, was born at 38+4 weeks of gestation. She had frequent spasm attacks accompanied by obvious psychomotor development retardation since the neonatal period. Genetic screening identified a novel STXBP1 genetic mutation.

Diagnoses: Early-onset epileptic encephalopathy with STXBP1 mutation.

Interventions: We adjusted the antiepileptic strategy to oral levetiracetam and topiramate, and intravenous administration of adrenocorticotropic hormone(ACTH) for 2 weeks. Subsequently, prednisone was continued, and gradually reduced and withdrawn over 3 months.

Outcomes: The treatment was effective with complete control of the epileptic seizures and improvements in the electroencephalogram readings. However, the effects on psychomotor ability were slow and limited. A literature review of STXBP1 mutation cases in which ACTH was administered showed that complete seizure control is observed in 60% of cases, 20% are partially affected, and the remaining 20% show no effect.

Lessons: ACTH and levetiracetam had good therapeutic effects in epilepsy control in this case of de novo STXBP1 mutation. ACTH is an effective drug for early-onset epileptic encephalopathy caused by STXBP1 mutation. However, controlling epilepsy using this therapy does not alter the psychomotor development retardation caused by the STXBP1 mutation.

Abbreviations: ACTH = adrenocorticotropic hormone, EESB = early epileptic encephalopathy with suppression bursts, EIEE = early infantile epileptic encephalopathy, GABA = gamma-aminobutyric acid, IS = infantile spasms, OS = Ohtahara syndrome, STXBP1 = syntaxin-binding protein 1, VEEG = video electroencephalography.

Keywords: adrenocorticotropic hormone, levetiracetam, STXBP1 encephalopathy

1. Introduction

Early-onset epileptic encephalopathy refers to continuous and repeated epilepsy accompanied by abnormal brain electrical activities in the neonatal or early infant period, which can lead to retardation of progressive cognition and comprehensive motor development.[1] Recent gene sequencing studies have found an increasing number of pathogenic genes associated with early-onset epileptic encephalopathy. In 2008, the syntaxin-binding protein 1 (STXBP1) gene was proved to be associated with early-onset epileptic encephalopathy.[2] STXBP1 encephalopathy is caused by an abnormal STXBP1 protein encoded by the mutated STXBP1 gene. Typical characteristics of the disease are epileptic seizures and severe psychomotor development retardation that occurs within 3 months of age, usually accompanied by low muscle tension, tremble, myoclonus, spastic quadriplegia or diplegia, stereotypical movement of the head or limbs, movement disorder, and ataxia. Currently, it is believed that STXBP1 encephalopathy is a type of complex neurodevelopmental disorder rather than primary epilepsy.[3] We report a case of STXBP1 encephalopathy caused by a de novo STXBP1 genetic

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[a] Department of Pediatrics, West China Second University Hospital, [b] Key Laboratory of Obstetric and Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education, Sichuan University, Chengdu, Sichuan, China.

[*] Correspondence: Xiao Tang Cai, Department of Pediatrics, West China Second University Hospital, Sichuan University, No. 20 Ren min Nan Road, Chengdu 610041, Sichuan, China (e-mail: cxt_1999@126.com).

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mutation, and review treatment effects of adrenocorticotropic hormone (ACTH) and levetiracetam as previously reported in the literature.

2. Case report

The patient, a girl, was born at 38^{+4} weeks of gestation with a birth weight of 2650 g; her Apgar score was normal. The patient's mother had a normal pregnancy, but she had a history of spontaneous abortion. There was no family history of seizure disorders, genetic metabolic disease, and mental illness. Ethical approval was obtained from the ethics committee of West China Second University Hospital, Sichuan University. Written informed consent was obtained from the parents of the patient for publication of this case report.

The patient had her first spasm seizures 6 days after birth that manifested as sudden nodding, lifting of double upper limbs and adduction of lower limbs, lasting for a second. She was treated at a local hospital with calcium and Vitamin D, but there was no significant improvement. The seizures gradually increased and

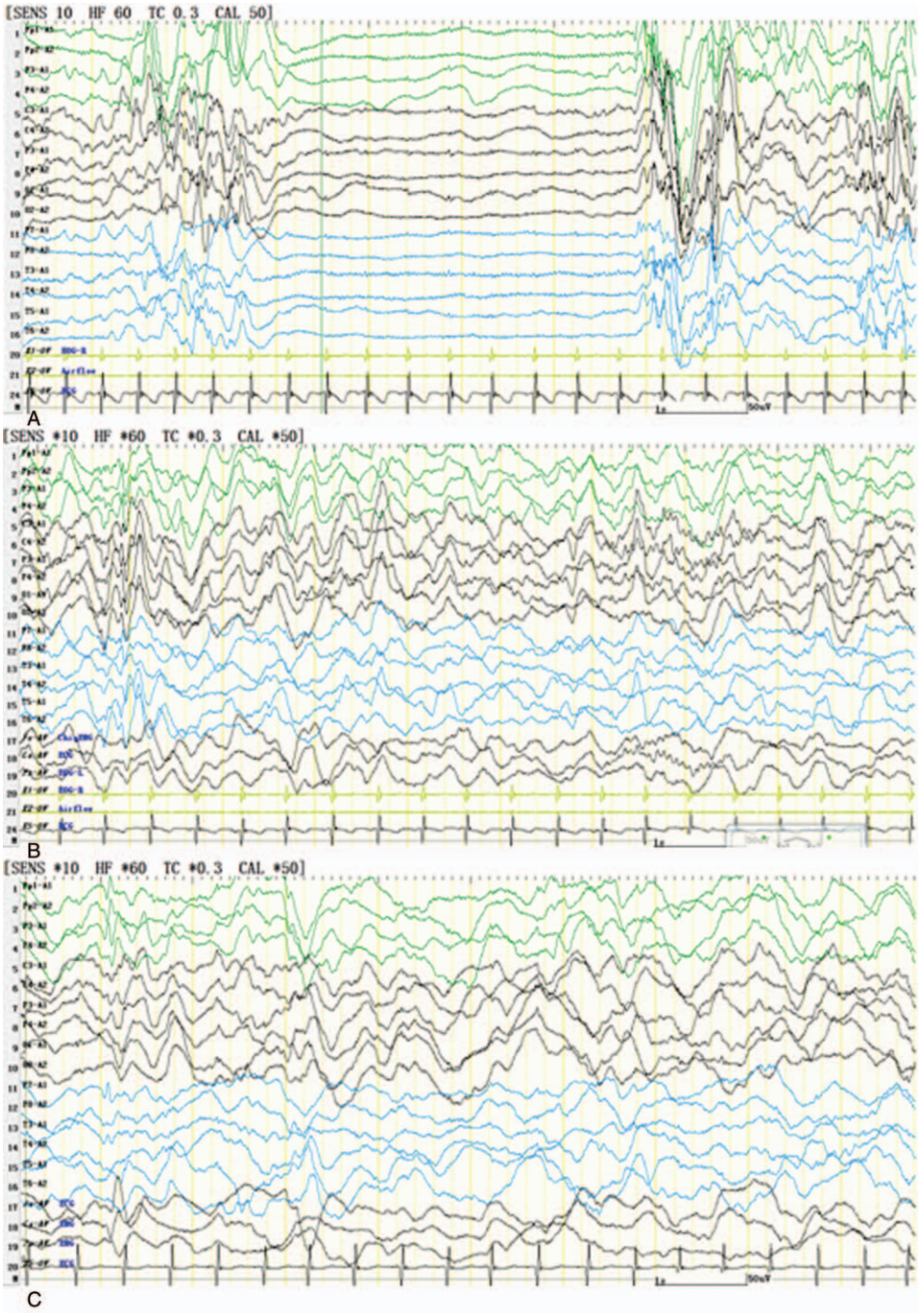

Figure 1. VEEG changes after ACTH treatment. (A) VEEG burst suppression pattern in the patient at the age of 2 months and 20 days, before ACTH treatment. (B) VEEG at the age of 3 months and 15 days, after ACTH treatment. Unilateral or bilateral sharp or spikes were observed in the forehead, frontal, central, parietal, and occipital regions. (C) VEEG performed at the age of 5 months and 15 days.

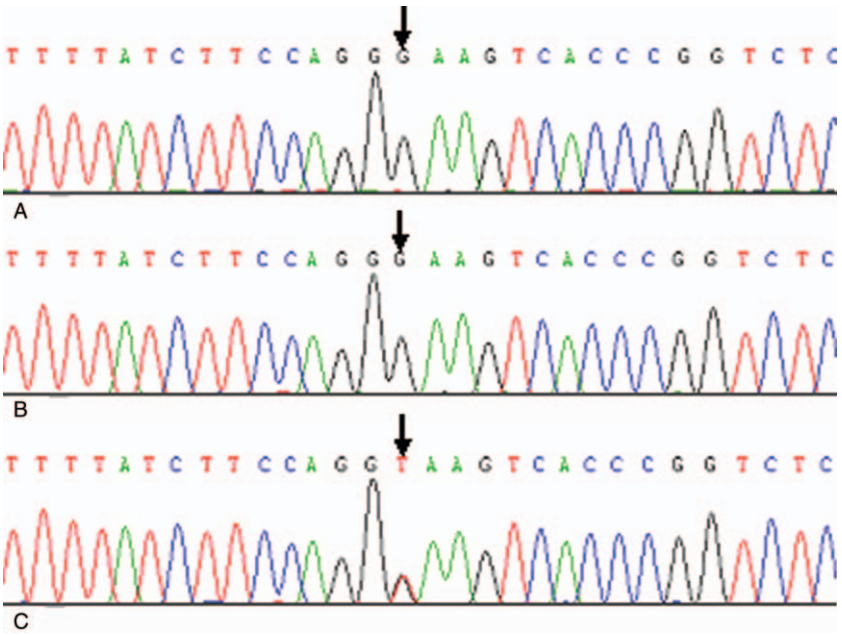

Figure 2. The STXBP1 gene mutation in the present case: location: chr9: 130432178-130432178, variant: NM_003165, nucleic acid: c.904G > T (exon 11), amino acid: p.E302X.302 (NM_003165), de novo truncation mutation. The mutation is heterozygous, and parents show a wild type allele.

became a cluster of spasm seizures, and the patient had seizures of more than 7 to 8 clusters/day, both while being awake and sleeping (about 50 times/day).

The patient was admitted to our hospital (West China Second University Hospital of Sichuan University, Chengdu, Sichuan, China) at the age of 2 months and 17 days. Physical examination revealed the following: head circumference: 38 cm, anterior fontanel: 3.5 cm × 3.5 cm. The patient was unable to chase light and objects, laugh, and raise her head. Muscle strength in the lower extremities was normal, but autonomous activity was reduced. The distal muscle tone was decreased but the knee tendon reflex was normal, and the patient had no positive Babinski sign or organomegaly. Laboratory tests revealed that complete blood counts and blood biochemistry (gas analysis, electrolyte, ammonia, lactate, pyruvate, and blood β-hydroxybutyric acid level) were normal. Additionally, liver and kidney function tests, hematuria tandem mass spectrometry, and brain magnetic resonance imaging revealed no abnormalities. Video electroencephalography (VEEG) indicated burst suppression pattern (Fig. 1). Initially, valproic acid (20 mg/kg), topiramate (5 mg/kg), and vitamin B6 (40 mg/kg) were administered daily for a week; however, seizures did not reduce. Next, valproic acid was replaced with levetiracetam (20 mg/kg per day). Seizures decreased from 7 to 8 clusters/day to 2 to 3 clusters/day (about 20 times/day) after treatment with levetiracetam and topiramate for 1 week. Further, intravenous administration of adrenocorticotropic hormone (ACTH 25 u/day) in combination with levetiracetam, topiramate, and high-dose vitamin B6 was performed. After ACTH use for 4 days, seizures were completely controlled. The patient could chase light and objects, and laugh following ACTH use for 2 weeks, but still could not raise her head independently. VEEG was performed again, and showed signs of improvement (Fig. 1).

After the girl was discharged from the hospital, prednisone (1 mg/kg/day) was continued, but was gradually reduced and withdrawn over 3 months. At the same time levetiracetam was gradually increased to 40 mg/kg per day and was accompanied with topiramate (5 mg/kg per day).

Further, whole exome sequencing test revealed mutations in the STXBP1 gene (located on chromosome 9) and truncated c.904G>T (exon 11) and amino acid p.E302X.302 (NM_003165); however, the parents showed a wild type allele (Fig. 2). Copy number variation was normal. Topiramate was gradually withdrawn, and levetiracetam was continued after mutations in the STXBP1 gene were revealed. The patient had no further seizures and could raise her head at the age of 6 months. Presently, at the age of 9 months, the patient's muscle tone is still slightly decreased, and she cannot sit by herself. Although she can laugh and chase sound better than she could before, she cannot speak single syllables like "da" and "ma".

3. Discussion and conclusions

In 2008, the STXBP1 genetic mutation was initially discovered by Saitsu H in a patient with Ohtahara syndrome (OS).[2] The STXBP1 gene, a member of the evolutionarily conserved Sec1/Munc-18 gene family, mainly encodes a specific membrane transporter protein in the brain, which plays a key role in the connection and integration of synaptic vesicles—an important mechanism of neurotransmitter secretion.[4] The lack of its expression may lead to damage of the synaptic vesicles and neurotransmission function, which greatly reduces readily releasable vesicles in GABAergic neurons (gamma-aminobutyric acid, GABA) compared with glutamatergic neurons, thus leading to excessive neural network excitement and epileptic activity.[5–7]

A total of 147 types of STXBP1 genetic mutations have been reported so far, including nonsense mutations, truncated mutations, and deletions. Currently, the correlation between genotype and clinical phenotype has not been established. In this case, the patient had a novel truncation mutation that has not been reported yet, and the normal codon encoding glutamic acid was mutated to a termination codon, 302 amino acids of the

Table 1

Summary of ACTH effects on patients with STXBP1 mutations, as reported in the literature.

Patient No.	Patient Sex	STXBP1 mutation	Diagnosis	Age at onset	Initial symptoms	Initial EEG	Age at onset of SB/HS pattern	Drugs	Development	Epilepsy evolution	Magnetic resonance imaging
1[25]	M	c.388_389delCT	EESB	2 m	Secondary generalized seizures initiated from the right face	SB with fluctuated baseline	2 m	ACTH/VPA	No head control, no social contact	Seizure free after ACTH	Normal
2[25]	F	c.663+5G>A	EESB	5 d	Blinking to tonic seizures	SB with fluctuated baseline	1 m	VB6/ACTH	Eye pursuit and smiling from 4 m, Head control and rolling over from 6 m	Seizure free after ACTH	Normal at 0 m, subdural effusion at 2 m
3[25]	M	c.961A>T p.K321X	EIEE	2 w	Partial seizures	SB	1 m	ACTH/drug resistance	No head control, no social contact/profound MR, severe spastic quadriplegia	Intractable seizure	Normal at 0 m. Brain atrophy and subdural hematoma at 7 m after ACTH
4[7]	M	C.963+?_(1967+?)	IS	4.5 m	Epileptic spasms	HS	4.5 m	VGB/NTZ/ACTH/VPA	Subtle hypertonia and ataxia, severe mental retardation	Seizure free at 8 m	Increased left frontal extracerebral space (4.5 m), normal fellow-up MRI (2 y 5 m)
5[11]	M	4-bp (ACTC) deletion in exon 4	IS	4 m	Growth retardation	Normal at 5 m HS at 6 m	6 m	ACTH/TPM/TRH/LTG/ corpus callosotomy	No head control, no social contact, social response has improved after surgery at 1 y 1 m	Seizure free at 6 m after ACTH. Relapse at 9 m, Seizure free after surgery at 1 y 1 m	Hypoplastic thin corpus callosum, delayed myelination of the cerebral white matter, and moderate atrophy of bilateral frontal lobes were apparent
6[10]	-	del exon8–14	OS	3 d	Epileptic spasms/ Tonic seizure	Some spikes in posterior regions/ fast rhythms	2 m	Steroids/ACTH/VGB	7 y: no walk, no speech	Seizure free 6 m	Normal
7[24]	F	c.902+5G>A	OS	37 d	Brief tonic spasms	SB	37 d	PB/Zonisamide/VPA/ KD/ACTH	No head control, no smile	Partially effective after ACTH	Normal
8[8]	F	del ex8-14	EESB/IS (2 m)	3 d	Tonic spasms	SB	3 d	VGB/HC/ACTH	12 y: Profound MR. No language, good eye contact	Seizure free 6 m	Thin and dysmorphic CC. Normal myelinization. Frontal cortical atrophy. Normal CT scan at 6 m. Normal spectroscopy
9[26]	F	c.1303G>T	IS	1 m	Generalized tonic seizures	Normal at 1 m HS at 4 m	4m	Drug resistance/ACTH	3 y: Turning over and sitting, no communication	Seizure free after ACTH	2 y 6 m:hypomyelination in the white matter
10[28]	F	c.1347del	IS	10 d	Epileptic spasms	HS at 5 m	5m	ACTH	2 y 6 m: bedridden, no communication	Seizure free after ACTH	2 y 6 m:brain volume loss
11[27]	M	chr9:130438188 (C>T) c.1216C>T/p.R406C	IS	3 m	spasms	HS	3m	ACTH/TPM/VPA. Then TPM/VPA and ketogenic diet	3 y 10 m: severe ID	Refractory seizures	Arachnoid cyst
12[29]	M	chr9:130438188 (C>T) c.1216C> T/p.R406C	OS	3 m	Spasms	Intermittent SB during sleep cycle	3m	VPA/ACTH	1 y: moderate ID	Refractory seizures	Ventriculomegaly
13[29]	-	9q33-q34 microdeletion	IS/ myoclonic epilepsy	3 m	Spasms, myoclonias;	HS	3m	ACTH and ZNS effective	Severe MR, hypotonia, motor dyspraxia, strabismus	Seizure free 8 m	Normal
14[28]	F	9q33-q34 microdeletion	EIEE	4 m	Spasms	SB	4m	VitB6/ZNS, ACTH, VPA/ NZP/KD ineffective; IVIG and CLB effective	Severe ID, axial hypotonia, limb hypertonia, status dystonicus in infancy, rotator nystagmus	Partially effective after ACTH but relapsed	Cortical atrophy, thin CC
15[Our case]	F	c.904G>T	EESB	6 d	Epileptic spasms	SB	2 m	VPA/LEV/LTG/ ACTH/steroid	No head control, no social contact, head control at 6 m, social response at 7 m	Seizure free at 3 m	Normal

ACTH=adrenocorticotropic hormone, CC=corpus callosum, CLB=clobazam, CT=Computer tomography, d=day(s), EEG=electroencephalography, EESB=early epileptic encephalopathy with suppression bursts, EIEE=early infantile epileptic encephalopathy, F=female, HC=hydrocortisone, HS=hypsarrhythmia, ID=intellectual disabilities;VGB=vigabatrin, IS=infantile spasms, IVIG=intravenous immunoglobulin, KD=ketogenic diet, LEV=levetiracetam, LTG=lamotrigine, M=male, m=month(s), MR=mental retardation, MRI=magnetic resonance imaging, NTZ=nitrazepam, OS=Ohtahara syndrome, PB=phenobarbital, SB=suppression bursts, TPM=topiramate, TRH=thyroxin-releasing hormone, VB6=vitamin B6, VPA=valproate, VPA=valproic acid, w=week, y=year(s).

protein sequence were shortened and thus contributing to the pathogenesis of the disorder. The parents of the patient did not carry this mutation; therefore, it is a de novo mutation.

Currently, increasing number of studies have demonstrated that epilepsy and psychomotor retardation are 2 major manifestations of neurological dysfunction caused by STXBP1 genetic mutation.[8,9] It is known that 95% of cases with the STXBP1 genetic mutation have epilepsy and early-onset epileptic encephalopathy, including OS, infantile spasms (IS), early epileptic encephalopathy with suppression bursts (EESB), and early infantile epileptic encephalopathy (EIEE).[2,8,10–12] Detection rates of the STXBP1 mutation in OS, West syndrome, and unclassified early-onset epilepsy encephalopathy are 21%, 9.5%, and 53%, respectively.[13] In 2010, Deprez[7] found that about 10.2% of patients with early-onset epilepsy encephalopathy had an STXBP1 mutation, suggesting that this was an important gene for early epilepsy encephalopathy. In the present case, the patient showed frequent spasm attacks 6 days after her birth that presented as sudden nodding, lifting of both upper limbs, and adduction of lower limbs. The attack progressed to cluster, and VEEG showed a burst suppression pattern.

The second major manifestation of the STXBP1 genetic mutation is psychomotor retardation.[8,14] All patients with STXBP1 genetic mutations show varying degrees of psychomotor retardation, with 90% displaying severe psychomotor development retardation and 17% having autism and autism-like spectrum disorder. However, no specific abnormalities are observed on cranial imaging and metabolic screening for the majority of these children. Psychomotor retardation can appear as an independent clinical manifestation or along with epilepsy.[8,13,15] In our case, epilepsy was fully controlled by the age of 3 months, and VEEG showed improved patterns. Throughout the follow-up visits, until the age of 9 months, no convulsion seizures were observed, but psychomotor retardation and low muscle tone had not significantly improved through epilepsy control. Our case confirms that levetiracetam and ACTH can reverse the epileptogenic abnormalities, but may not be effective in altering the accompanying psychomotor development retardation caused by an STXBP1 gene mutation.

According to previous reports, the treatment of STXBP1 encephalopathy was comprehensive, including epilepsy control and neurological rehabilitation. Studies have demonstrated that epilepsy in about half of the patients could be controlled after drug administration; however, over half of the children needed treatment with 3 antiepileptic drugs. Several studies report that vigabatrin, valproic acid, topiramate, clobazam, oxcarbazepine, and ketogenic diet were effective in seizure control.[8,16–21] Levetiracetam was also reported to have a good effect.[8,22,23] In the present study, no obvious effect was seen on epileptic seizures when topamax and valproic acid were used. The frequency of seizures reduced after using levetiracetam, but could not be fully controlled, suggesting that levetiracetam was partially effective. Levetiracetam regulates synaptic vesicle release system by binding to the synaptic vesicle protein SV2A, which regulates synaptotagmin-1. Lou et al[24] reported that synaptotagmin-1 is an antagonist for Munc18–1 in SNARE zippering. Thus, levetiracetam binds to and regulates SV2A, and may counterbalance the epileptogenic effects induced by STXBP1 mutation. [22,23] Nonetheless, these studies were based on a small number of cases, and there was no large prospective study available for verification.

With regard to the therapeutic efficacy of ACTH, we reviewed 15 reports of patients carrying an STXBP1 mutation treated with ACTH in the literature.[7,9,11,12,25–30] and compared the therapeutic efficacy of ACTH (Table 1).[7,8,10,11,24–29] Among them, 4 cases were diagnosed with OS, 6 cases had IS (1 case later evolved to infantile myoclonic epilepsy), 3 cases had EESB (1 case later evolved to IS), and 2 cases had EIEE. With the exception of ACTH, 2 patients did not use any antiepileptic drugs (AEDs), 5 patients used 1 AED, while 8 patients used 3 or more AEDs. Steroid, ketogenic diet, IVIG, and surgery were used in 3, 4, 1, and 1 case, respectively. Although the sample size is small, ACTH was effective in controlling seizures; 9 cases showed complete seizure control (Patients 6 and 8 used vigabatrin at the same time), 3 cases showed partial seizure control (Patient 5 had seizure control after ACTH but relapsed 3 months later, and was seizure-free after surgery. Patient 14 had seizures disappear after ACTH but relapsed soon, seizures decreased after treatment with intravenous immunoglobulin and clobazam), and 3 cases showed no effect (Patient 3, 11 were multidrug resistant). In this case, we demonstrate seizure control with improved VEEG patterns after ACTH treatment and no seizure relapse throughout the follow-up for 7 months. Combined with previous cases reports, we conclude that ACTH is an effective drug for epileptic seizure control in early-onset epileptic encephalopathy caused by an STXBP1 mutation.

Briefly, in cases of early-onset epileptic encephalopathy and severe psychomotor development retardation, the STXBP1 gene should be considered as a candidate for early genetic screening. Early application of levetiracetam and ACTH may provide therapeutic benefits for epilepsy.

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Author contributions

Conceptualization: Xiao T. Cai.
Project administration: Shunli Liu, Liyuan Wang.
Resources: Dan Yu.
Supervision: Hui Zhou, Zhiling Wang.
Validation: Hui Zhou.
Writing – original draft: Shunli Liu.
Writing – review & editing: Liyuan Wang, Xiao T. Cai.

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