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FULL-LENGTH ORIGINAL RESEARCH

Epileptic and nonepileptic features in patients with early onset epileptic encephalopathy and *STXBP1* mutations

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Summary

Purpose: ***STXBP1 (MUNC18-1)*** **mutations have been associated with various types of epilepsies, mostly beginning early in life. To refine the phenotype associated with *STXBP1* aberrations in early onset epileptic syndromes, we studied this gene in a cohort of patients with early onset epileptic encephalopathy.**

Methods: ***STXBP1*** **was screened in a multicenter cohort of 52 patients with early onset epilepsy (first seizure observed before the age of 3 months), no cortical malformation on brain magnetic resonance imaging (MRI), and negative metabolic screening. Three groups of patients could be distinguished in this cohort: (1) Ohtahara syndromes (n = 38); (2) early myoclonic encephalopathies (n = 7); and (3) early onset epileptic encephalopathies that did not match any familiar syndrome (n = 7). None of the patients displayed any cortical malformation on brain MRI and all were screened through multiple video–electroencephalography (EEG) recordings for a time period spanning from birth to their sixth postnatal month. Subsequently, patients had standard EEG or video-EEG recordings.**

Key Findings: **We found five novel *STXBP1* mutations in patients for whom video-EEG recordings could be sampled from the beginning of the disease. All patients with a mutation displayed Ohtahara syndrome, since most early seizures could be classified as epileptic spasms and since the silent EEG periods were on average shorter than bursts. However, each patient in addition displayed a particular clinical and EEG feature: In two patients, early seizures were clonic, with very early EEG studies exhibiting relatively low amplitude bursts of activity before progressing into a typical suppression-burst pattern, whereas the three other patients displayed epileptic spasms associated with typical suppression-burst patterns starting from the early recordings. Epilepsy dramatically improved after 6 months and finally disappeared before the end of the first year of life for four patients; the remaining one patient had few seizures until 18 months of age. In parallel, EEG paroxysmal abnormalities disappeared in three patients and decreased in two, giving place to continuous activity with fast rhythms. Each patient displayed frequent nonepileptic movement disorders that could easily be mistaken for epileptic seizures. These movements could be observed as early as the neonatal period and, unlike seizures, persisted during all the follow-up period.**

Significance: **We confirm that *STXBP1* is a major gene to screen in cases of Ohtahara syndrome, since it is mutated in >10% of the Ohtahara patients within our cohort. This gene should particularly be tested in the case of a surprising evolution of the patient condition if epileptic seizures and EEG paroxysmal activity disappear and are replaced by fast rhythms after the end of the first postnatal year.**

KEY WORDS: **Epilepsy, Suppression-burst, Genetic, Encephalopathy Ohtahara.**

Early onset epileptic encephalopathies (EOEEs) are severe conditions with epileptic seizures beginning within the first 3 months of life, associated with abnormal ictal and interictal electroencephalography (EEG) and variable cognitive deterioration. EOEEs can be caused by brain malformations, metabolic disorders, or associated with proved or suspected genetic defects. Within EOEEs, two epileptic

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syndromes have been described, in which the EEG traces display a specific interictal pattern called ''suppression-burst'' with high voltage spikes and sharp waves alternating with periods of flatness: (1) early myoclonic encephalopathy (EME) with predominant myoclonic jerks; and (2) Ohtahara syndrome, with predominant epileptic spasms (Aicardi & Ohtahara, 2005). The neurologic outcome is poor in both conditions, and knowing the etiology when brain magnetic resonance imaging (MRI) does not show any cortical malformation is still challenging.

Recently, Saitsu et al. (2008, 2010) reported *STXBP1* mutations in 14 unrelated patients from a cohort of 43 patients with Ohtahara syndrome in two distinct papers. The patients displayed early onset seizures, typically frequent epileptic spasms, suppression-burst pattern on EEG recordings, a transition to West syndrome after a few months in most cases, and severe developmental retardation. The authors showed that mutant proteins were degraded and concluded that *STXBP1* haploinsufficiency could be a major molecular marker of Ohtahara syndrome. However, other studies reported *STXBP1* mutations in other types of epilepsies: Early onset West syndrome in two cases (Deprez et al., 2010; Otsuka et al., 2010), nonspecific early onset epileptic encephalopathy in six cases (Hamdan et al., 2009; Deprez et al., 2010); and nonsyndromic mental retardation with or without epilepsy in two cases (Hamdan et al., 2009, 2011). To better assess the importance of *STXBP1* mutations in EOEEs with suppression-burst, such as the Ohtahara syndrome, early myoclonic epilepsy, and other EOEEs, we have screened this gene in a cohort of 52 patients. We found mutations of *STXBP1* in five patients, all displaying Ohtahara syndrome. Here, we describe their clinical, epileptic, and nonepileptic features.

Methods

Patient selection

Fifty-two patients were included in a cohort of subjects who had early onset epileptic encephalopathy with suppression-burst. Inclusion in the cohort was determined according to the following criteria; (1) onset of the epilepsy within the first 3 months of age; (2) abnormal interictal EEG displaying a ''burst-suppression'' pattern, that is, high-voltage generalized bursts with spikes and polyspikes, alternating with periods of flattening of the EEG, lasting 1–20 s (the suppression-burst pattern should be recorded in the absence of a high dose of phenobarbital); (3) brain MRI should not show any cortical malformation or hypoxic lesions; (4) all patients screened for metabolic disease (nonketotic hyperglycinemia, hyperammonemia, urea cycle defect, organic aciduria, hyperlactacidemia, pyridoxine-dependent and pyridoxal-dependent seizures). All patients displayed a major neurologic impairment.

For each patient, the epileptic syndrome was assessed using the classification of the International League Against Epilepsy (ILAE) (Berg et al., 2010). Among the 52 patients included in the cohort, 38 had Ohtahara syndrome, 7 had an early myoclonic encephalopathy, and 7 had early onset epileptic encephalopathy that could not be classified into one or other epileptic syndrome, that is, patients displaying either a suppression-burst pattern for <2 weeks, or an atypical suppression-burst, with asynchronous and/or brief periods of silence. Patients should be followed at least once a year by a pediatric neurologist to assess clinical and EEG data.

Patients came from several hospitals in France (Marseille, Dijon, Limoges, Paris, Lyon, Bordeaux, Toulouse, Tarbes, Tours, Rennes, and Montpellier). Informed consent was obtained from all individuals and/or their families. Epileptic and nonepileptic features were assessed using video-EEG.

Mutation screening

Genomic DNA was extracted from peripheral blood lymphocytes of all patients and their unaffected parents. The 20 exons of *STXBP1* were amplified using PCR and directly sequenced using flanking intronic primers (primer sequences are available upon request). When a mutation was identified, it was confirmed using a second sequencing run. Inheritance was assessed by comparison with the sequence of the parental DNAs. To search for microdeletions we used a custom made 72K Nimblegen CGH microarray containing targets corresponding to 2,200 exons of genes involved in glutamate metabolism, including known early onset epileptic encephalopathy genes (list and design available upon request). These arrays were hybridized, scanned, and analyzed according to the manufacturer's instructions (Roche Nimblegen, Madison, WI, U.S.A.).

Results

Five novel *STXBP1* mutations were found in the cohort (5 of 52, i.e., 10%). All mutations were heterozygous in the patient samples and occurred de novo. We found one intragenic microdeletion, one splicing mutation, and three missense mutations. All patients were unrelated.

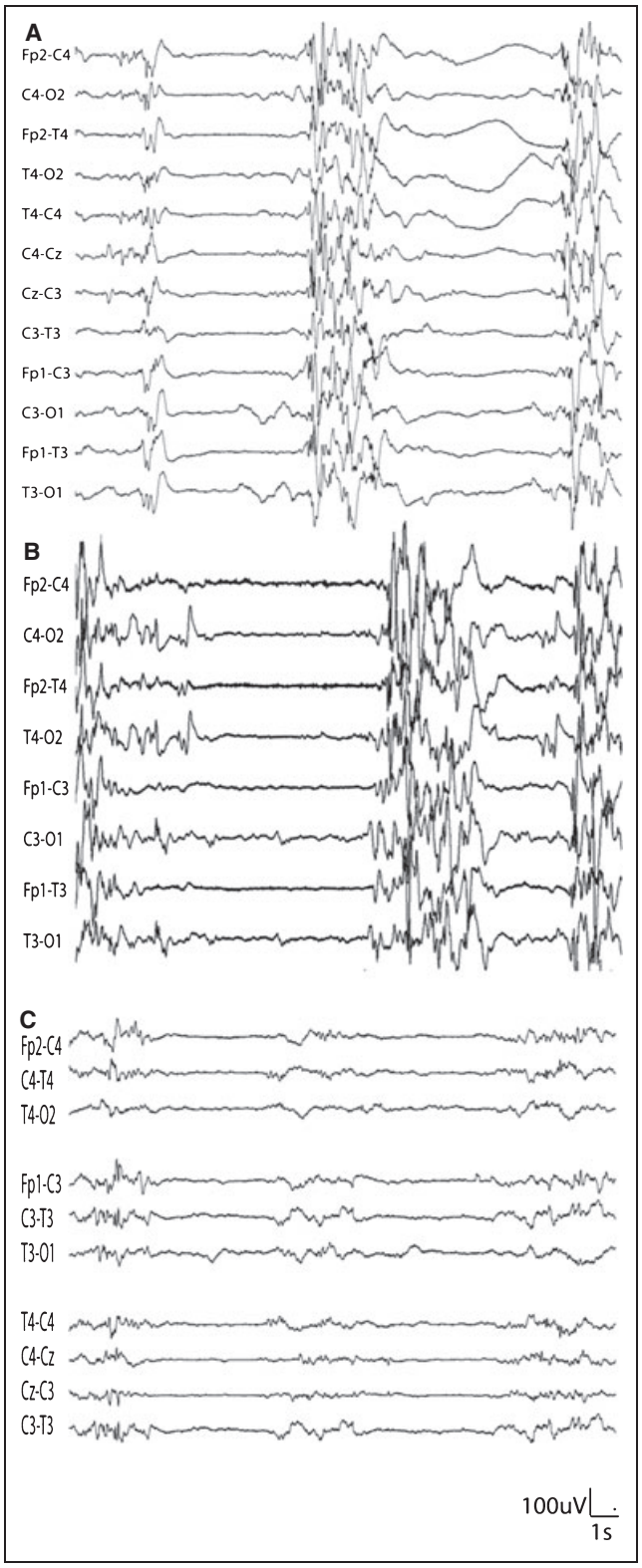
Epileptic and clinical features of patients with *STXBP1* aberrations

Among a cohort of 52 patients with EOEE, we first screened for *STXBP1* in 38 patients with an Ohtahara syndrome. We found an *STXBP1* mutation in five patients (13%) (Fig. S1, Table 1). All mutations/deletions were absent from the parental DNAs. None of the patients had any familial history of epilepsy. Pregnancy and delivery were normal in each case. We were able to review the first EEG/video recordings of four patients. In each case, bursts of activity were either asymptomatic or associated with sudden complex movements of the body axis, occurring in clusters (Fig. S2A,B, Video S1). These movements lasted several seconds, consisting of asynchronous contractions

Table 1. Summary of clinical features of patients with *STXBP1* mutation

Patient	*STXBP1* mutations	Age at first seizure	Clinical description of the first seizure	First clinical examination	Duration of the suppression-burst pattern	First month: main type of seizure	First year: antiepileptic drugs used	First year: seizure types	Epilepsy evolution	Nonepileptic movements	Clinical examination at the end of the follow-up
1	c.902+1G>A p.Q301fsX1	16 h	Clonic asynchronous	Hypotonia	6 weeks	Epileptic spasms	Vigabatrin steroids clonazepam	Epileptic spasms Focal seizures Generalized tonic–clonic seizures	Stop 18 months	Nonepileptic jerks Pedaling Dyskinetic hand movements Stereotypes hand movements	4 years Ataxic walking Autistic features No speech
2	c.1439C>T p.P480L	5 weeks	Epileptic spasms	Hypertonia	5 weeks	Epileptic spasms	Vigabatrin steroids clonazepam Topiramate	Epileptic spasms Tonic seizures	Stop 18 months	Jerks Dystonic postures Dyskinetic movements	2 years Axial hypertonia No sit
3	c.1720A>C p.T574P	1 day	Clonic asynchronous	Hypotonia	2 weeks	Epileptic spasms	Vigabatrin Valproate Levetiracetam	Epileptic Spasms Startles	Stop 12 months	Jerks Trembling Dyskinetic hand movements Stereotypic movements	4 years Ataxic walking Autistic features No speech
4	DEL exon8–14	3 days	Epileptic spasms	Hypotonia	2 months	Epileptic spasms	Vigabatrin Steroids ACTH	Startles	Stop 6 months	Jerks	7 years No walk No speech
5	c.548T>G p.L183R	1 day	Epileptic spasms	Poor eye contact Failure to thrive	3 months	Epileptic spasms Tonic seizures	Vigabatrin Clonazepam Valproate	Tonic seizures	Stop 6 months	Trembling	2 years Axial hypertonia Autistic features

of the axial muscles and were more complex than classical epileptic spasms. All patients displayed several types of seizures within their first year of life, including myoclonic jerks (2 of 5 patients with Ohtahara syndrome and a mutation of *STXBP1*), partial seizures (5 of 5), and clonic seizures (2 of 5). After the initial phase, seizure frequency gradually decreased in all patients and disappeared before the end of the first year of life in four patients (range 6–11 months). None of the patients had any epileptic seizure after the second year of age. The parents of one patient reported occasional epileptic seizures after the first year of life, but multiple video-EEG recordings failed to detect any seizure despite frequent nonepileptic movements. At the end of the follow-up period, patients displayed autistic features with stereotyped dyskinetic movements and poor eye contact. Hand use was effective for two patients with a trembling gripping. Language was absent in all patients. Three patients could walk from the age of 3.



EEG features of patients with *STXBP1* aberrations

A suppression-burst pattern could be recorded as early as the first performed EEG in three patients (Fig. 1A,B), whereas for the two additional ones, EEG initially displayed discontinuity, with periods of flatness alternating with bursts of paroxysmal activity with a lower amplitude that usually expected in Ohtahara syndrome (Fig. 1C). When patients were 1 month of age, the EEG indicated a suppression-burst pattern for all the patients. Periods of suppression lasted between 1 and 15 s. Bursts consisted of generalized spikes and waves that lasted from 1–20 s and were either associated with a startle, apnea, complex dystonic movements, or asymptomatic (Fig. S2A,B; Video S1). The suppression-burst pattern always persisted during sleep. In all patients, silence periods were on average shorter than burst periods. After 2 months of age, the suppression-burst pattern was progressively replaced by a more continuous one, with multifocal and asynchronous spikes and slow waves that could be rhythmic (Fig. 2A). A hypsarrhythmic pattern was observed for only one patient during sleep and wakefulness. For all the subjects, the EEG dramatically improved before the end of the first year of life. In three cases, paroxysmal activity could no longer be recorded, whereas the EEG of the two additional cases displayed some spikes in the anterior or posterior regions (Fig. 2B). Background activity was continuous, within the theta/alpha band and some periods of even faster activity could be observed (Fig. 2B). These fast rhythms were observed for all the five patients and persisted for the entire follow-up period.

Figure 1.
Different patterns of early EEG in patients with an *STXBP1* mutation. (**A**, **B**) Representative EEG showing classical suppression-burst pattern recorded in Patients 2 (**A**) and 5 (**B**), showing discontinuous EEG traces, with burst of paroxysmal activity alternating with periods of silence. Paroxysmal bursts were asymptomatic. (**C**) Representative EEG showing discontinuous EEG pattern recorded in Patient 3. Periods of flatness of the traces alternated with low amplitude bursts.

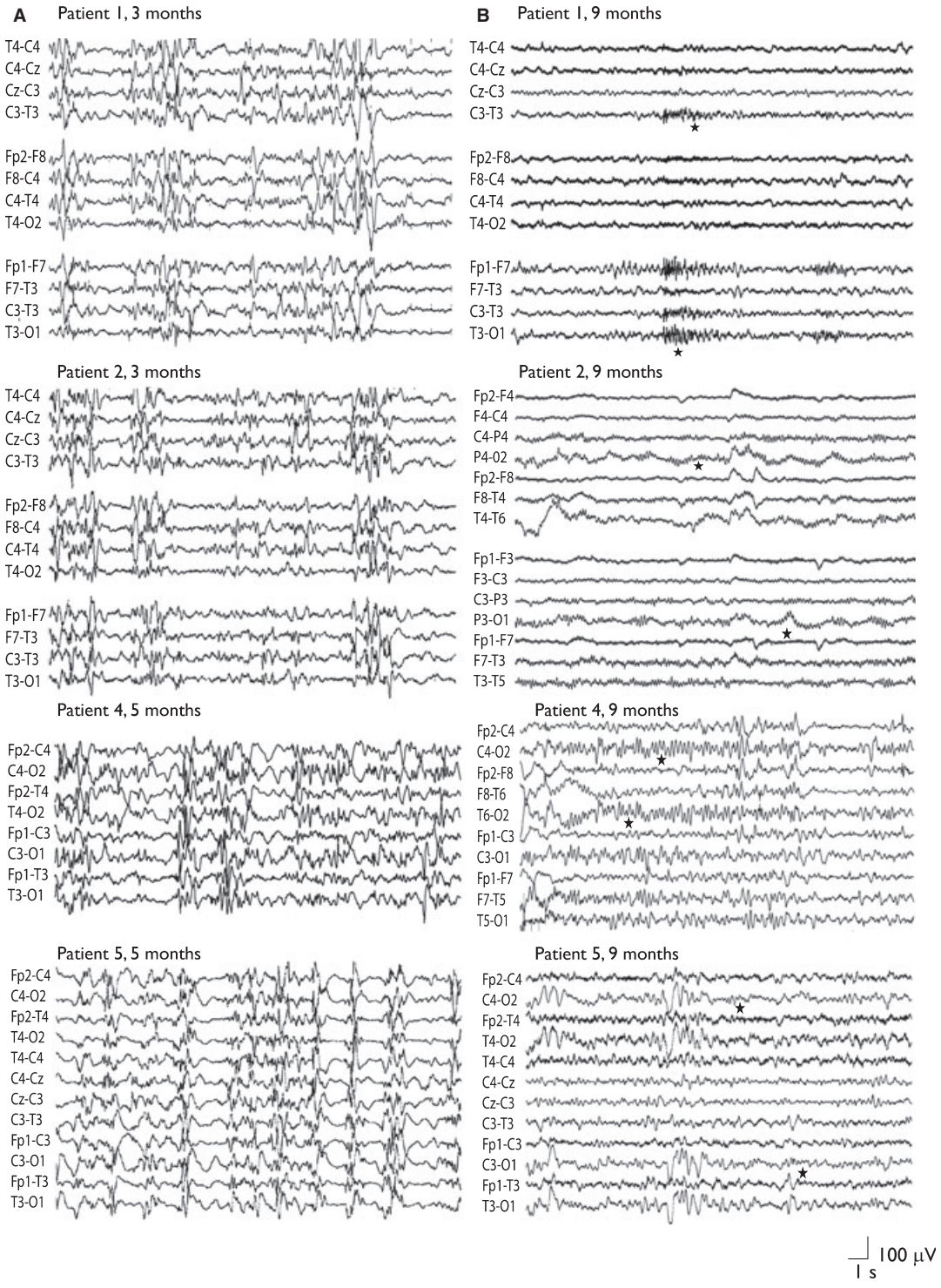


Figure 2.
Surprising evolution of the EEG pattern. (**A**) EEG recorded in four patients at 3 (Patients 1 and 2) and 5 months of age (Patients 4 and 5) during wakefulness. Note that EEG traces became more continuous but were still abnormal, with bursts of spikes and slow waves alternating with periods of flatness of the traces. (**B**) EEG recorded in same patients at 9 months of age during quiet wakefulness. Paroxysmal activity has disappeared in Patients 1 and 2, giving place to fast rhythms that were mostly recorded in posterior regions (stars). EEGs of Patients 4 and 5 showed some spikes that predominate in frontal (Patient 1) or posterior regions (Patient 5). Fasts rhythms were either discontinuous (Patient 1, 5) or continuous (Patients 2 and 4) and predominated in posterior regions.

Nonepileptic movements of patients with an *STXBP1* mutation

When reviewing all the video-EEG recordings from every patient, we were surprised to detect many paroxysmal motor sequences consisting of choreic axial movements, brief axial contractions, and rhythmic movements of one or more limbs that were not associated with any EEG modification (Fig. S3A, Video S2). These movements could be recorded nearly as early as birth. All patients also displayed dystonic postures and trembling episodes that could last several minutes, without any EEG modification. Some of these nonepileptic movements could easily be mistaken for epileptic spasms, since they consisted of axial contraction lasting ~1 s, occurring in clusters, and without any epileptic abnormality on the EEG (Fig. S3B, Video S3). In addition, after the second year of life, prolonged and repeated video-EEG recordings failed to detect any epileptic seizure despite the occurrence of frequent and stereotyped complex dyskinetic and choreic movements.

Comparison of clinical and epileptic features of patients with an Ohtahara syndrome with and without *STXBP1* aberrations

To find any clinical or EEG feature that could be specific for Ohtahara patients with an *STXBP1* mutation, we analyzed various electroclinical signs for the five patients with an Ohtahara syndrome and an *STXBP1* mutation versus 33 patients with an Ohtahara syndrome but no *STXBP1* mutation (Table 2). Whereas the initial phase was not specific, a rapid epilepsy and EEG improvement associated with predominant dystonic movements was systematically detected in patients with an *STXBP1* mutation (Table 2). *STXBP1* was normal for all cases of early myoclonic epilepsy and for the patients with an early onset epileptic encephalopathy that did not fit with any recognizable epileptic syndrome.

Table 2. Electroclinical features in patients with Ohtahara syndrome with or without mutation in *STXBP1*

	Ohtahara syndrome and *STXBP1* mutation, n = 5	Ohtahara syndrome No *STXBP1* mutation, n = 33
Age at onset of epilepsy (days)	8	17
First month	5 patients	33 patients
Main type of seizure	Epileptic spasms: 100%	Epileptic spasms: 100%
First EEG	Suppression-burst (SB): 60%	Suppression-burst: 70%
	Low voltage SB: 40%	Low voltage SB: 30%
At 1 year	5 patients	28 patients
Epilepsy recovery	4/5	3/28
No EEG paroxysmal activity	3/5	4/28
EEG fast rhythms	5/5	2/28

Discussion

This study provides further evidence that *STXBP1* is an important genetic determinant for EEOEs, specifically regarding the Ohtahara syndrome.

Saitsu et al. (2008, 2010) described five and nine patients with an Ohtahara syndrome and *STXBP1* mutations in two different papers. Neither the seizure type at onset nor the neurologic evolution differed from the five patients reported here. However, only two patients from their cohort did have West syndrome, whereas none of the patients reported here did. Furthermore, only three patients from Saitsu et al. became seizure-free, whereas it was the case for all the patients in our cohort. Epilepsy improved spontaneously since treatment was not modified. Therefore, *STXBP1* haploinsufficiency is a rather frequent cause of Ohtahara syndrome, independent from the evolution of the epilepsy (West syndrome or disappearance).

STXBP1 mutations are not specific to the Ohtahara syndrome. Hamdan et al. (2009) reported two de novo *STXBP1* mutations in 2 of 95 individuals with mental retardation and nonsyndromic epilepsy (2%). Deprez et al. (2010) identified six *STXBP1* aberrations in 106 patients with early onset epileptic encephalopathy. None of the mutation-carrying patients had an Ohtahara syndrome. One patient was diagnosed with a West syndrome at disease onset, whereas the initial phenotype of the five additional patients did not correspond to any specific epilepsy syndrome. These studies provide further evidence that classification of early onset epileptic encephalopathies remains a challenging task, and that the presence of a ''suppression-burst'' pattern may not be specific to any underlying mechanism of epileptogenesis.

Several common points can be identified in the five patients with *STXBP1* mutations described here:

All patients displayed abnormal nonepileptic movements that began early and that were still present at the end of the follow-up period. These movements were heterogeneous and difficult to distinguish from epileptic movements without any video-EEG recording. In all five cases, nonepileptic movements were probably more frequent than epileptic seizures. Moreover, they persisted for the entire follow-up period, whereas the incidence of epileptic seizures rapidly decreased or disappeared. The presence of such nonepileptic movements was not classically reported in patients with Ohtahara syndrome or any other early onset epileptic encephalopathy and could be a key clinical feature for identifying good candidates for *STXBP1* screening in Ohtahara syndrome.

All patients but one became seizure-free before the end of the first postnatal year. This feature is rather surprising, given the severity of the initial epilepsy phase. Antiepileptic drug treatment could be completely stopped in three patients; one patient was seizure-free with 0.1 mg of clobazam per day. The remaining patient had frequent

nonepileptic movements that were not associated with any EEG abnormality (myoclonic jerks, spasms, and so on); her parents occasionally described epileptic seizures that could never be recorded in video-EEG. She still receives two antiepileptic drugs (topiramate and clobazam).

In all cases, paroxysmal EEG abnormality was almost completely replaced by a general slowing of the EEG, superimposed by generalized or localized fast rhythms, with some patients displaying rare spikes (Fig. 1B,C). Such evolution of the EEG signal is rather surprising for this type of epileptic syndrome, and had not been described before.

To date, to our knowledge, 29 different mutations of *STXBP1* have been described, for which 28 patients were epileptic (Fig. 1), including the five novel mutations we report. Nineteen patients had Ohtahara syndrome, five patients had an early onset epileptic encephalopathy, two had an early onset West syndrome, and two had nonsyndromic epilepsy with mental retardation (Saitsu et al., 2008; Hamdan et al., 2009; Deprez et al., 2010; Otsuka et al., 2010; Saitsu et al., 2010). One patient had intellectual disability without any epilepsy (Hamdan et al., 2011). Interestingly, among epileptic patients, all missense mutations described to date gave rise to an Ohtahara syndrome, whereas nonsense, splice mutations, and deletions were associated with Ohtahara syndrome (seven cases), early onset epileptic encephalopathy (five cases), West syndrome (two cases), or nonsyndromic mental retardation (one case).

In conclusion, STXBP1 should be screened in cases of EOEE, even if early epileptic features are rapidly replaced by nonepileptic ones.

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Disclosure

None of the authors has any conflict of interest to disclose. 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.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Mutations of *STXBP1* in patients affected by Ohtahara syndrome, early onset epileptic encephalopathy, West syndrome, and mental retardation with nonsyndromic epilepsy.

Figure S2. EEG activity during early paroxysmal motor activity in two patients.

Figure S3. Nonepileptic, dyskinetic movements were frequently observed in all patients.

Video S1. Representative example of motor activity that could be recorded during bursts of paroxysmal EEG activity (Patient 1, 3 months, see also Fig. S2B).

Video S2. Sequences of dyskinetic movements were also observed in all patients from the beginning to the end of the follow-up.

Video S3. Some paroxysmal movements consisting in axial contractions occurring in cluster were recorded.

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