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Case Study

Epilepsy is not a mandatory feature of *STXBP1* associated ataxia-tremor-retardation syndrome

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ABSTRACT

Background: Mutations in the *STXBP1* gene (*MUNC18-1*) were first described to cause Ohtahara syndrome (Early infantile epileptic encephalopathy, EIEE)[12–14] characterized by very early infantile epileptic encephalopathy with frequent tonic spasms and a suppression-burst pattern on electroencephalogram. In the following years a wider phenotype was recognized having milder forms of epilepsies. All patients showed also intellectual disability and movement disorders.

Methods: Here, we present three female patients with an ataxia-tremor-retardation syndrome caused by a *de novo STXBP1* mutation. Two of the girls were diagnosed through next-generation-sequencing as mutations in *STXBP1* were not suspected. The third patient was diagnosed by targeted genetic testing due to its clinical features strikingly similar to the first two girls.

Results: The characteristic feature of our three patients is the lack of epilepsy which is in contrast to the majority of the patients with *STXBP1 mutation*.

Conclusion: Hence, epilepsy is not a mandatory feature of patients with a *STXBP1 mutation*.

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1. Introduction

De novo mutations in *STXBP1* have been found in a group of patients with early infantile epileptic encephalopathy (EIEE), the so-called Ohtahara syndrome[12–14]. The Ohtahara syndrome is characterized by a severe early infantile epileptic encephalopathy. It usually starts in the first three months after birth and shows a characteristic burst-suppression EEG pattern. Tonic spasms are the predominant seizure type. The epilepsy is severe and refractory to anticonvulsive treatment.

The etiology of Ohtahara syndrome is heterogeneous and includes metabolic diseases like nonketotic hyperglycemia, malformation of the brain and mutations in various genes such as *STXBP1, KCNQ2, KCNT1, SLC25A22, GNAO1, ARX or CDKL5*. All patients suffer from severe developmental delay and severe neurologic pathology like muscular hypotonia or spasticity and motor asymmetries. The prognosis is poor with a high mortality rate during infancy. A high proportion of patients with Ohtahara syndrome transit to West syndrome characterized by epileptic encephalopathy with epileptic spasms and hypsarrhythmia.

Saitsu and coworkers[12] identified mutations in the *syntaxin-binding protein 1 (STXBP1)* gene, which encodes *Munc18-1*, in patients with Ohtahara syndrome. In following studies it was recognized that the epileptic phenotype of *STXBP1 mutations* is broader and not limited to Ohtahara syndrome[2,3]. Some patients with Dravet syndrome were also shown to have *STXBP1 mutations*[1] whereas other patients presented with an atypical epilepsy syndrome partly starting later in childhood and responding better to anticonvulsive treatment.[3] For that reason the suppression burst pattern on EEG was no longer considered as a mandatory feature of *STXBP1* related encephalopathy.

Additional behavioral disturbances such as hyperactivity, stereotypic behavior, hand biting and hyperventilation burst were frequently recognized in affected patients.

A variety of associated movement disorders like ataxia, tremor and head tremor were also described in patients with *STXBP1 mutations*.[2,6,9,15] Furthermore, common signs of severe encephalopathy of diverse course, e.g. spasticity, muscular hypotonia, choreoathetosis and dyskinetic limb movements were found in many patients. However, spasticity was not reported in patients without EIEE.[8]

Hamdan et al.[4] reported the first patient with intellectual disability caused by a *STXBP1 mutation* who did not develop epilepsy. So far, infantile-onset epilepsy was the most consistent criterion for the selection of patients to investigate the *STXBP1 gene*. Rauch et al.[10] found *STXBP1 mutations* in 3% with severe non-syndromic sporadic intellectual disability in an exome sequencing study. Unfortunately, it was not reported how many of these patients presented without epilepsy. Stamberger et al.[15] recently reviewed the phenotypic spectrum of a cohort of 147 patients with STXBP1-mutations including 45 previously unreported patients. Nine of this patients had intellectual disability without epilepsy.

2. Patients

Here we report on three female patients with intellectual disability caused by a *de novo STXBP1 mutation* (Table 1). None of the three female patients did develop epileptic seizures until the age of 12, 11 and 9 years. When we had the knowledge of the diagnosis we asked the parents if the children might have had subtle seizures in the past maybe during the neonatal period or later. But they denied. EEGs earlier and at the time of diagnosis were unconspicuous. EEGs were performed at different ages and showed an age-related slowing but never any sings of increased risk for epilepsy.

All three of our patients had severe developmental delay and neurologic pathologies but they are not as severely affected as patients with epileptic encephalopathy. Therefore their phenotype differs to the so far described patients with *STXBP1 mutations*. Despite the lack of epileptic features, all three girls showed the characteristic triad of symptoms including ataxia, tremor and intellectual disability. We thus postulate a broader phenotype of the ataxia-tremor-retardation-syndrome caused by *STXBP1 mutations* without epilepsy.

Due to its uncharacteristic clinical manifestation we did not consider *STXBP1 mutations* underlying this phenotype. Elaborated clinical and diagnostic tests were performed including MRI, EEG, neurometabolic and genetic testing that did not identify the underlying cause of the disease. In all three girls Angelman-Syndrome was a likely diagnosis because of overlapping feature: severe intellectually disability, severe expressive language problems and ataxia. Patient I was diagnosed through whole exome sequencing, patient II through TruSight ONE, looking for ID genes described by Stephen Kingsmore which is a panel on the basis of the clinical exome.[5]

Patient III was referred to our clinic by the parents of patient II, as the two girls (patient II and III) attended the same class at a special school. They were not related to each other but their parents claimed that they behaved like twins. Not only that they both had intellectual disability, the way they moved was similar, they showed similar mood-swings and a similar way to communicate. They both spoke only single understandable words but a lot of syllables without understandable sense. Because of the similar phenotype, targeted genetic testing was done in patient III and indeed showed a *de novo mutation in STXBP1*.

Although all three girls had striking clinical similarities, they did not present with any dysmorphic features. Their gestalt fits into the respective family characteristics. Pregnancy, birth and neonatal period were normal in each girl. Family history was more or less unremarkable. First developmental abnormalities were recognized between the age of 4 (patient II) and 7 month (patient III). All three patients presented with muscular hypotonia and psychomotor delay as their first symptoms. Patient I and II also had head tremor already as a newborn which disappeared later in life. The development of all three girls was delayed but did not have any signs of regression. They started walking between the age of 2 ½ (patient III) and 3 ½ years (patient II) of life. They all presented with an action tremor of the arms and hands, and with peculiar tremulous finger movements while handling with objects. All three also had an atactic gait from the beginning with frequent falls but without progression. They had no oculomotor abnormalities like a