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Case Report

STX1B-related epilepsy in a 24-month-old female infant

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ABSTRACT

We report on a 24-month-old girl with age-appropriate development and normal intellectual ability suffering from myoclonic astatic epilepsy. Panel-based sequencing of roughly 1500 genes associated with neurodevelopmental and metabolic diseases identified a heterozygous *de novo* point mutation in *STX1B* (c.733C>T or p.Arg245*). *STX1B* encodes Syntaxin-1B which plays a role for synaptic transmission. *STX1B* variants are associated with a broad phenotypic spectrum of epilepsies including febrile or afebrile seizures as well as epileptic encephalopathies. Our patient with MAE adds to the spectrum of *STX1B* associated phenotypes.

1. Introduction

Epilepsy is one of the most common neurological diseases. In Germany, the annual incidence is around 60 in 100.000 in children, with a peak in the first year of life [1]. Approximately 70–80% of all epilepsies have a genetic origin [2]. Hereditary epilepsies are often classified into three groups: generalized, focal and epileptic encephalopathies.

Myoclonic Astatic Epilepsy (MAE) belongs to generalized epilepsies, which is also known as Doose syndrome [3]. MAE has an incidence of 1 in 10.000 children, accounting for approximately 1–2% of childhood-onset epilepsies [4]. Within the first year of life the incidence is equal for both genders, while it is more common in males later on [4]. Astatic seizures are characterized by a sudden loss of muscle tone followed by a forward or backward fall, often resulting in head injuries [5]. Myoclonic seizures are defined as quick jerking movements that occur truncally or axially [4]. Therapeutic management strategies focus on antiseizure medication, preferably as a monotherapy, e.g. with levetiracetam. Further options are ACTH and induction of a ketogenic diet [4]. Despite frequent seizures, patients with MAE often have good cognitive outcomes. It is reported that up to 90% have normal intellectual ability or minor cognitive impairment [4]. A ketogenic diet usually leads to successful treatment of seizures.

Family history plays an important role in MAE. Previous publications reported that seizures occurred in 35–40% of relatives of individuals with MAE [3,6]. The prevalence of myoclonic and astatic seizures among family members was about 2%, which is 200 times higher than in the general population [7]. Multifactorial inheritance is very likely in this condition. Although pathogenic sequence variants have been identified in the *STX1B*, *SCN1A, SCN1B, SLC2A1* and *GABRG2* genes, the cause of MAE remains unknown in most patients [8].

2. Case report

We present a 24-month-old Caucasian girl (weight 10.9 kg (27. percentile), height 87.4 cm (69. percentile), head circumference 47 cm (18. percentile)) who was born after normal pregnancy and spontaneous delivery as the first child of German parents. Two generalized clonic seizures followed by focal motor seizures a few days later occurred at the age of 14 months.

The first seizure happened during night in early March 2019. The girl was found unconscious by her mother, twitching her arms and legs, without cyanosis and salivation. After approximately one minute, the child was responsive to physical stimulation and speech and cried immediately. The next day, the girl was sitting in her high chair and suddenly tipped back. For about 10 s, her arms and legs were twitching and she was rigid, again without cyanosis and increased salivation. The ambulance was called and, on arrival, the seizure had already terminated. Body temperature was not elevated on both events.

The child had just recovered from an upper airway infection with fever up to 39.6 °C the week before. Influenza A and Parain-

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fluenza were tested positive. The girl had received antibiotic therapy (cefaclor) because of otitis media a week before seizures.

The initial EEG showed a mixed delta-theta-activity between 2–3 and 4–7/s and a voltage amplitude between 30 and 150 μV, occasionally slightly superimposed by flat and quick alpha-activity. The slow delta-activity was accentuated on the left hemisphere. Furthermore, focal grouped spike and spike-wave complexes were seen on right parietal and right temporal areas as well as on the vertex. On the left central regions some spikes and spike waves were found as well (Fig. 1). While the EEG was performed, no clinical seizure was observed. The initial EEG was evaluated as pathologic, most likely as an infantile epilepsy with secondary generalized tonic clonic seizures.

Medication with levetiracetam was started. In order to rule out the differential diagnosis of a parainfectious or metabolically related encephalopathy, blood tests and a lumbar puncture were performed. In the CSF there was absence of any infectious markers (Borrelia burgdorferi, Enterovirus, HSV 1 and 2, Influenza 1 and 2, Mycoplasma). Cell count, glucose, lactate and Albumin were normal. There was no evidence of oligoclonal bands. The CSF culture showed no bacterial growth. An extended metabolic screen of the CSF showed no defect of pterin metabolism and only unspecific changes of amino acids. An MRI scan of the brain was performed and showed a slight enlargement of the cisterna magna while the rest of the subarachnoid space was normal (Fig. 2). No epileptiform discharges were discovered and there was no evidence of brain malformation.

During therapy with levetiracetam the girl still had several generalized tonic-clonic seizures of short duration (between 10 s and 4 min). These seizures were accompanied by cyanosis, hypersalivation and smacking. The girl also had astatic seizures with sinking of the head and forward falls of the upper body as well as myoclonic fasciculation in the facial area accompanied by staring and wailing. Due to these events, anticonvulsive treatment was replaced by valproic acid. Based on the type of seizures and EEG findings, her epilepsy was classified as early onset epilepsy with generalized tonic-clonic seizure and MAE. During therapy with valproic acid the EEG currently shows no evidence of epileptic potentials. Currently, her epilepsy is well controlled. The girl develops age-appropriately (50th percentile of the MFED development evaluation, "Münchener Funktionelle Entwicklungsdiagnostik", Munich Functional Developmental Diagnostics [9]) with normal intellectual ability. She visits a normal day care center. She speaks 2-word sentences and her motor skills are age appropriate as well.

Family history revealed that her father had seizures at the age of 16 and 36 years, respectively. The first event was an astatic seizure with subsequent unconsciousness for about 30 s. After the first event, antiseizure medication with levetiracetam was started and maintained for ten years. This was followed by a seizure-free period of another ten years without medication, until a second seizure occurred, which was reported as a generalized tonic-clonic event. Antiepileptic treatment with levetiracetam was started again up to date. An initial MRI scan of the brain showed edema of the left parahippocampal gyrus and the left cornu ammonis. Limbic encephalitis or a low-grade glioma were initially considered. However, the unchanged follow-up scans rather suggest unspecific alterations.

Apart from that the family history was unremarkable, especially regarding seizures and epilepsy.

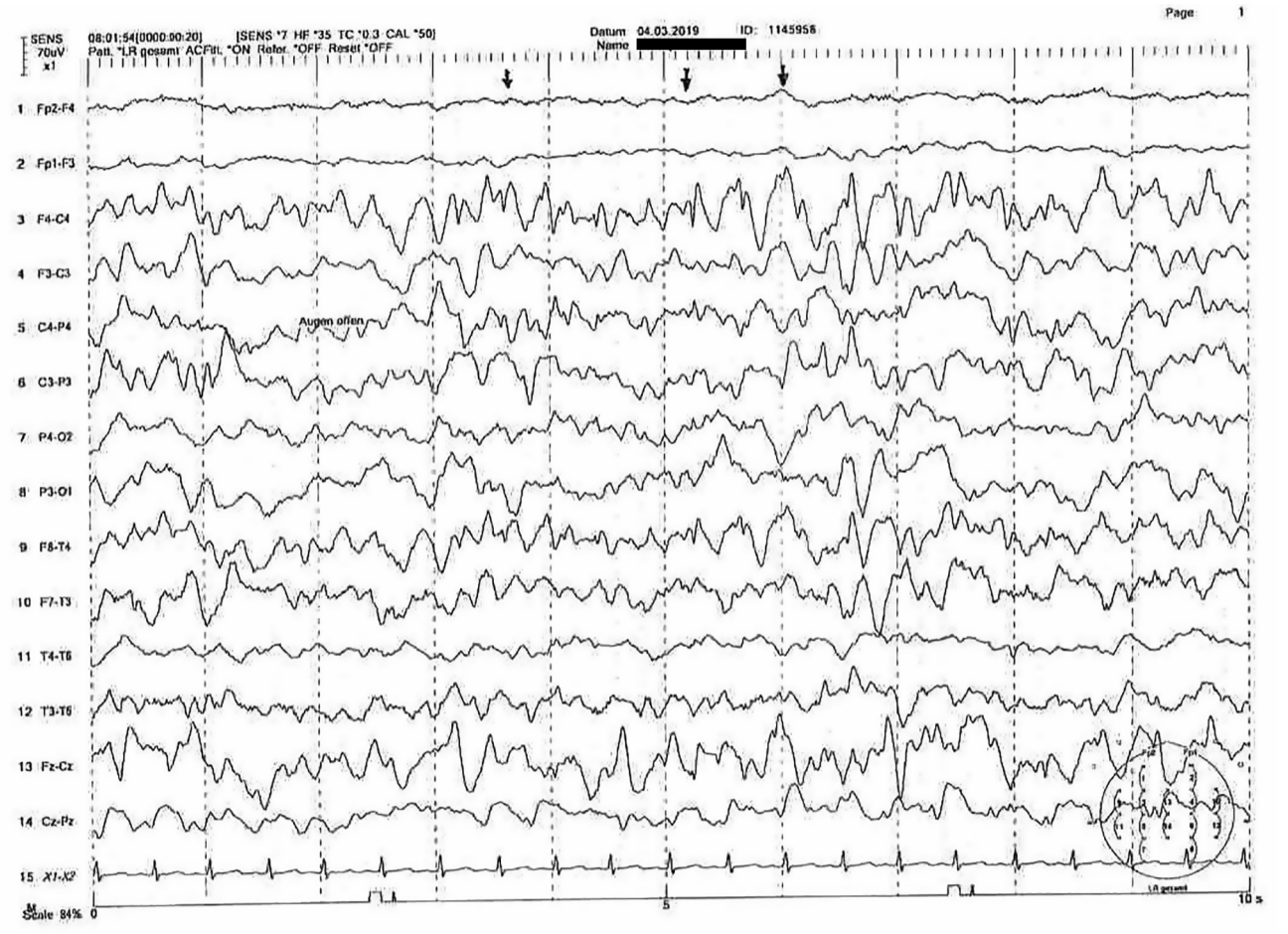

Fig. 1. Initial waking EEG of the patient (March, 4th 2019):

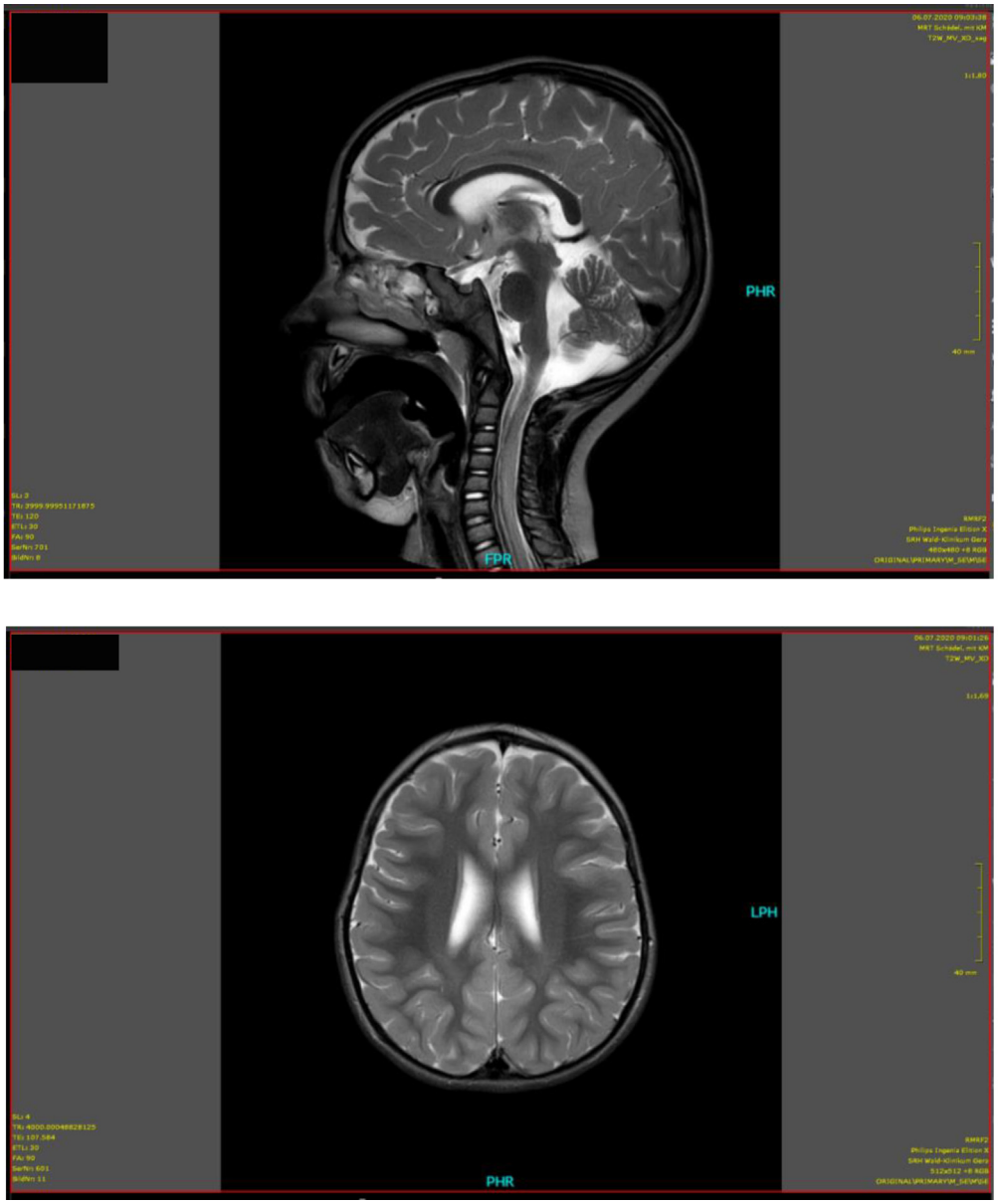

Fig. 2. MRI scan of the brain (sagittal, coronal) (July, 6th 2020):

Parents were offered a genetic test for their child. Next-generation sequencing (Agilent SureSelectXT respectively Agilent SureSelectXT Human All Exon V7, IlluminaR sequencing technology) was performed. The coverage of reported variants achieved at least 20-fold sequencing depth. As a result of a "Master Panel", which included more than 1500 genes related to neurological and metabolic diseases, a heterozygous *STX1B* variant c.733C>T (p.Arg245*) with clinical relevance was discovered. According to the ACMG-classification the variant was classified as likely pathogenic (class 4).

The parents were offered a targeted genetic test of the *STX1B* variant. The *STX1B* variant was absent in both parents thus suggesting a de novo event in the affected girl.

3. Discussion

We found a pathogenic *STX1B* de novo variant in a 24-month-old child with myoclonic astatic epilepsy (MAE) and normal intellectual ability. The *STX1B* gene (Locus 16p11) encodes the presynaptic protein Syntaxin-1B [10]. Syntaxins are cellular receptors for vesicle transport. Syntaxin-1B is a presynaptic protein which is a part of the SNARE complex mediating calcium-dependent synaptic vesicle release [11]. Wolking et al. described 17 different variants in *STX1B* in patients with epilepsy including one patient with the c.733C>T (p.Arg245*) variant identified in our patient.

The (c.733C>T) exchange is located on the second last exon (exon 9) of *STX1B* and entails a premature termination codon. Because it is located 54 bp upstream of the 3′ exon–exon junction it may result in nonsense-mediated decay (NMD) [12]. Essential factors for the pathogenesis of epilepsies are abnormal cellular excitability leading to changes in membrane depolarization and repolarization as well as abnormal synchronization of neuron clusters. Deletion of STX1B in mice results in severe seizures and premature lethality combined with dysfunctional release of neurotransmitters at glutamatergic and GABAergic synapses [13]. It is assumed, that a triggering mechanism is a lack of coordination of neuronal excitation and inhibition resulting in a disturbed com-

munication of the neuronal network. *STX1B*-related epilepsy could be caused by an imbalance between the excitatory effect of glutamate or aspartate and the inhibitory effect of GABA.

Regarding genetics and epilepsy, a de novo variant in a single gene is a typical finding in patients with infantile epilepsies [14]. Less than 10% of genetic epilepsies are found to be inherited in a recessive manner [15]. A mutation discovered in a patient with epilepsy helps to classify its etiology as hereditary. However, it should be considered that there is a broad phenotypic heterogeneity in most of the epilepsy genes, meaning that a mutation does not necessarily lead to a certain type of epilepsy or epilepsy at all [16]. In many cases a certain mutation alone does not have phenotypic consequences, however, additional environmental factors or other susceptibility variants might eventually result in epilepsy [16].

In general, the reason for genetic testing in patients with epilepsy is trying to identify the cause of the epilepsy, having an accurate diagnosis and finding the best medical management. For some hereditary epilepsies, seizures may be expected to stop at a certain age which may help to decide to discontinue anti-seizure medication. Results of genetic testing can be used to test family members at risks, as well as the risk of having a child with epilepsy.

Because there is no single test that can diagnose all genetic epilepsies and there is considerable variation from laboratory to laboratory, a panel approach or even exome analysis should be considered at an early time point. It is suggested that not only children with severe epilepsies but all newly diagnosed early-life epilepsy patients should undergo broad genetic testing [15].

Vlaskamp et al. reported on a patient with a *STX1B* variant that did not have febrile seizures prior to epilepsy onset [17]. Their patient suffered from myoclonic astatic seizures, similar to our patient. Lerche et al. reported on a large five-generation German family with *STX1B* mutations in which 18 individuals experienced early-onset febrile and/or afebrile seizures [18]. Furthermore, Weber and colleagues reported on another four-generation German family with *STX1B* mutations in which eight individuals had various forms of febrile and/or afebrile seizures [19]. Together, these findings support the hypothesis that *STX1B* is not only involved in the etiology of fever-associated epilepsies [10,18,19], but also in the etiology of non-fever-related epilepsies, including MAE.

The study of Wolking et al. expanded the number of reported patients with *STX1B*-related epileptic syndromes and described 17 novel variants [10]. This highlights the importance of considering this gene in panels for epilepsy.

Our finding of a *STX1B* variant in another patient with MAE, in addition to the patient reported in Wolking et al. [10] suffering from afebrile seizures and MAE, suggests that afebrile seizures and MAE may be part of the *STX1B*-related epilepsy spectrum. The *STX1B* gene should therefore be considered in the diagnostic workup of epilepsies in patients with a similar phenotypic presentation.

Ethical Statement

The authors declare their compliance with all relevant ethical regulations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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