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CASE REPORTS

De novo *STXBP1* mutation in a child with hypotonia, intellectual disability, tremor and without epilepsy

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Abstract

Syntaxin-binding protein 1, encoded by STXBP1, is widely expressed in the brain and plays a critical function in regulating neurotransmitter release and synaptic vesicle fusion by binding to and altering the conformation of syntaxin-1A (STX1A). According to the previous reports, pathogenic loss-of-function mutations in this gene cause a variety of different forms of epilepsies, the majority of which occur during childhood. There may also be spasticity, dystonia, tremors, choreiform and stereotyped movements, ataxia, and hypotonia. The disease's phenotypical spectrum remains unknown. We report here a de novo mutation (c.1162C > T: p.R388X) in exon 14 of the STXBP1 gene that causes muscular hypotonia, speech and walking delays, intellectual disability, and tremors in a 5-year-old boy. Brain magnetic resonance imaging was normal. This variant was identified as de novo (maternal and paternal confirmed). This is the first Turkish report of a patient with a truncating mutation in *STXBP1* that does not show epilepsy, thus expanding the clinical spectrum associated with *STXBP1* gene disorders.

Keywords: Epilepsy, intellectual deficiency, mutation, tremor, *Syntaxin binding protein 1 (STXBP1)*

INTRODUCTION

The syntaxin-binding protein 1 (STXBP1) gene is located on 9q34 and encodes the STXBP1 protein through 20 exons.[1] According to studies, the STXBP1 protein transports syntaxin-1 to the plasma membrane in a closed shape, facilitating vesicle fusion.[2] Nearly 300 patients with intellectual disability, epilepsy, and movement problems have been documented to have heterozygous harmful mutations in the STXBP1 gene.[3] The clinical manifestations from the mutant spectrum includes West syndrome, an undefined early-onset epileptic encephalopathy, Dravet syndrome, intellectual disability without epilepsy, autism, and childhood-onset ataxia.[4]

We present a patient with hypotonia, intellectual disability, developmental delay, aphasia, and resting tremor but without epilepsy, who was found to have a de novo pathogenic STXBP1 mutation.

CASE REPORT

The proband was presented to our pediatric neurology outpatient clinic at the age of 5 years for developmental delay, speech disturbance, and hypotonia. He was a male who was born at 38 weeks of pregnancy to a 25-year-old mother by cesarean section. The parents were not consangineous. He had an uneventful birth and postnatal period. He started to sit when he was four years old.

The examination revealed a head circumference of 52.5 cm + 2 SD. He did not speak; instead, he communicated through pointing, but he exhibited a severe tremor when reaching for something. When he was called, he made eye contact. The deep tendon reflex (DTR) was hypoactive, and the Babinski sign was flexor bilaterally. He was unable to stand without assistance. The brain MRI was normal (Figure 1). Electroencephalography showed no abnormalities.

The laboratory findings, including the blood count, electrolytes, thyroid function tests, creatine kinase, and B12 vitamin level, as well as the detailed metabolic investigation (urine and blood amino acids, carnitine-acyl carnitine measurement with tandem mass, urine organic acid analysis, and

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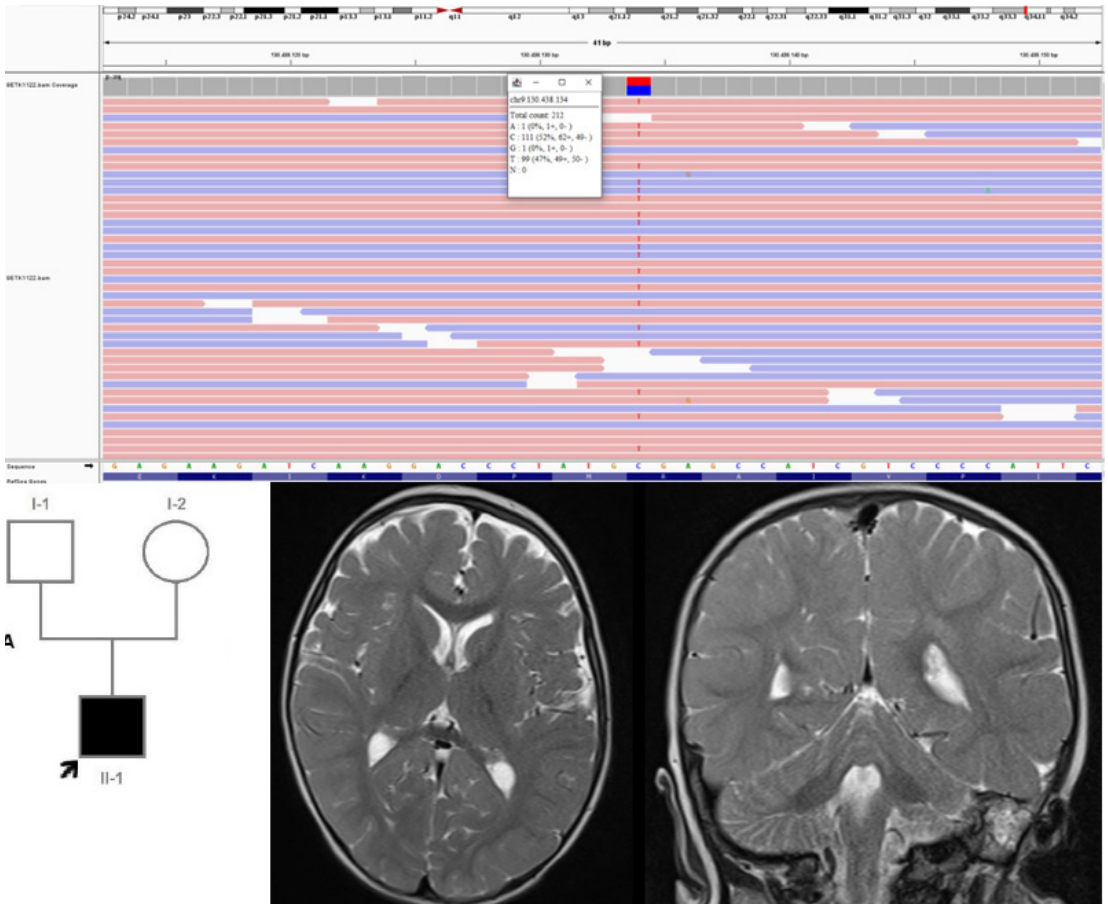

alpha-fetoprotein), were all normal. Lactate concentration was 45.8 mg/dL (4.5-20), amonia concentration was 83 g/dL (31-123), and pvruvate concentration was 0.41 mg/dL. (0.3-0.7).

Karyotype analysis of G-banding indicated a normal 46, XX karyotype. *The SMN1* gene (including deletion and duplication testing) identified no causative variants. An Agilent Oligonucleotide microarray with the 8X60k probe was used to investigate for copy number variants in a DNA sample obtained from peripheral blood. The results were analyzed in the Agilent cytogenomic 5.0.0.38/grch37/hg19 analysis program. Microarray analysis revealed that it was normal. The next-generation sequencing of the mitochondrial DNA genome was also normal. Whole-genome sequencing of a DNA sample from our patient was performed by MGI (DNBSEQ-G400). The data analysis using the Genemaster analysis programme revealed a novel heterozygous mutation in the STXBP1 gene, NM_001032221;c.1162C>T(p.R388X)(Figure 1).

Segregation analysis revealed that the clinically unaffected parents carried a wild-type allele. This mutation was not observed in either the ESP6500 public or 1000genome databases and was predicted to be pathogenic by PolyPhen-2, SIFT, and Mutation Taster tools. Phenotype-genotype analysis indicates that the variant has a significant effect on the development of the disease. Informed consent was obtained from the parents.

DISCUSSION

So far, nearly 300 *STXBP1* genetic mutations have been reported, including nonsense mutations, truncated mutations, and deletions.[5] In this case, the patient had a truncation mutation, which resulted in the substitution of a termination codon for the normal arginine codon. As a result, the protein sequence was shortened by 388 amino acids, contributing to the disorder's pathogenesis. Because the patient's parents did not carry this mutation, it is a de novo mutation. Epilepsy and psychomotor retardation are two prominent features of neurological dysfunction caused by the STXBP1 genetic mutation, as previously

demonstrated.[6] According to Deprez *et al*.[7], approximately 10.2% of patients with early-onset epilepsy encephalopathy had a STXBP1 mutation, indicating that this gene was involved in early epileptic encephalopathy. In the largest series of patients with the STXBP1 mutation, epilepsy was detected in 95% and intellectual disability without epilepsy was detected in 6% (9/147), as in our patient.[8] We suggest that STXBP1 mutations should be considered not only in patients with epileptic encephalopathy, but also in the patients with developmental delay and intellectual disability. We describe a de novo truncating mutation c.1162C > T: p.R388X. As far as we know, our case is the first in the literature to present with developmental delay, tremor, and mental retardation without epilepsy due to the STXBP1 (c.1162C > T) mutation. Hamdan *et al*.[9] identified this mutation as pathogenic in a 15-year-old female patient with severe intellectual disability and non-syndromic epilepsy. The STXBP1 c.1162C > T: p.R388X mutation was previously described in another study as a pathogenic variant in a proband with early developmental delay and epileptic encephalopathy.[10]

Değerliyurt *et al*.[11] reported a patient presenting with infantile epileptic encephalopathy, seizures, ataxia, tremor, intellectual disability, and an *STXBP1* mutation. *STXBP1* is a master regulator of neurotransmitter release that enables syntaxin 1A to engage in the SNARE complex. *STXBP1*-related disorders are well characterized by encephalopathy with epilepsy and a diverse range of neurological and neurodevelopmental conditions.[12]

The STXBP1-E phenotype is caused by loss-of-function mutations in STXBP1 that effect synaptic vesicular transport and the release of neurotransmitters that interact closely with the SNARE proteins. Previously published reports have all failed to establish a clear link between phenotype and genotype in patients with STXBP1 mutations. While the genetic variants underlying the clinical phenotype can be identified directly, their relationship to the protein stability, interactions, and dynamics of the cellular processes involved in synaptic function remains unknown.[12,13]

Our patient's MRI findings were normal. Sharkov *et al*. described a 10-month-old boy with cortical dysplasia and epilepsy. Meglio *et al*. studied 24 STXBP1-mutant patients. All the patients except one had normal MRI findings. However, one patient's cortex in the right parietal area had an irregular shape that was not associated with any signal change.[14]

In conclusion, it is unknown what relationship exists between STXBP1 gene mutations and their phenotypic effects. With newly reported cases and mutations, the phenotypic spectrum of STXBP1 encephalopathy remains unknown. STXBP1 encephalopathy should be considered in the presence or absence of epilepsy in cases of intellectual disability, hypotonia, speech delay, and tremors.

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DISCLOSURE

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Conflict of interest: None

Data availability: All data generated or analysed during this case report are included in this article. Further enquiries can be directed to the corresponding author.

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