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LETTER TO EDITOR

Familial Hyperekplexia in Two Sisters: An Unusual but Treatable Neuropediatric Entity

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Hyperekplexia is primarily an autosomal dominant disorder characterized by an exaggerated startle reflex and neonatal hypertension. If untreated, it may be associated with sudden infant death syndrome due to apnea or aspiration pneumonia and severe injury. Several mutations of the 1-subunit of the inhibitory glycine receptor (GLRA1) have been found. In addition, mutations were found in the genes GLRB, GPHN, and, in our case, two sisters SLC6A5. Clonazepam, a gamma-amino-butyric acid (GABA) receptor agonist, is the treatment of choice. Early diagnosis leads to appropriate treatment and genetic counseling.

We report of a family with 5 children. The father is 43-years-old and the mother is 37-years-old. The family came to Germany from Syria in 2015 and has been living in Germany for one year as initiators of diagnostic treatment. The mother described rhythmic intrauterine movements in the 4th month of pregnancy. These movements were also found in the 13-years-old sister. N., the five-years-old girl, had seizures for four months of her life. The time of seizures lasted from 1 minute to 2 hours initially. In Syria, phenobarbital, valproate, and levitiracetam were given. Further treatment in Germany consisted of 200 mg carbamazepine in the morning and evening in an outpatient setting. Semniological analysis of the seizures revealed a tonic-clonic form, lateral tongue bites, open eyes, variable timing, approximately 2 minutes. EEG analysis in Germany in 2016 revealed normal sleep EEG, no epileptic potentials. Further EEG analyses later were without pathological signs. Vitamin B6 treatment was administered (3 × 140 mg daily). Clinical neurological evaluation revealed global hyperreflexia without pyramidal symptoms. Molecular analysis revealed a homozygous stop variant in the SLC6A5 gene. The other sister, A., 13 years old, a good student, does not attend school sports because of fear of suddenly falling down, hearing loud noises and voices. She had an episode of loss of bonus in moments of loud noises and voices. She is on monotherapy with valproate. EEG analysis revealed a right-sided occipital focus with spike-wave activity without photosensitivity. Molecular analysis revealed a known homozygous variant in the SLC6A5 gene. Discussion Hyperekplexia is based on muscular hypertonia and overwhelming responses to tactile stimuli and is defined as a

neurogenetic childhood disorder. Kirsten and Silfverskiold referred to the disorder as "emotionally precipitated drop seizures [1]. Neonates with hyperekplexia show diffuse muscular hypertonia, hyperreflexia, and startle responses to sounds and voices. Disruptive reactions may be elicited by tipping to the labelage region. Hypertonia and hyperreflexia relieves at the end of 1 year of life. Motor development is delayed to fear falls. Cases are described in the literature of children walking on their knees to avoid falling over suddenly. In 1992, the autosomal dominated hyperekplexia gene was found in a linkage study on the long arm of chromosome 5 (5q33-35) [2,3]. A homozygous mutation of the SLC6A5 gene was found in both children. This result is phenotypic evidence for hyperexplexia. SLC 6A gene codes for presynaptic glycol transporters. The gene affects extracellular glycol concentration in neurotransmission setting. In hereditary hyperekplexia, symptoms were found in the early neonatal period with seizures with hypertonicity of the musculature. In both children, the pathological homozygous variant of c. 861 C A; p. Tyr287 was found in the SLC6A5 gene. This mutation has consequences for both children: fear of athletic activation due to decreased activity; fear of loud noises and consequent loss of muscle tone. Benzodiazepine treatment is the treatment of choice in this severe single gene mutation condition.

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