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LETTER TO THE EDITOR

Neuropsychiatric manifestations in hyperekplexia: A case with a novel *SLC6A5* variant

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Dear Editor,

Hyperekplexia is a rare neurodevelopmental disorder characterized by exaggerated startle responses to tactile or auditory stimuli and neonatal hypertonia, most commonly inherited in an autosomal recessive pattern (1). It results from dysfunction of the glycinergic inhibitory system and is frequently linked to mutations in the *GLRA1, GLRB*, and *SLC6A5* genes. *SLC6A5* encodes the presynaptic glycine transporter 2 (GlyT2), and mutations in this gene are associated with more severe phenotypes, including life-threatening apnea (2). Importantly, beyond its motor manifestations, hyperekplexia has also been reported to be associated with a range of neuropsychiatric features, including global developmental delay (GDD), intellectual disability (ID), learning difficulties, and speech and language impairments (3). These findings highlight the need for a multidisciplinary approach and underscore the importance of child psychiatric evaluation in the comprehensive assessment and long-term management of affected patients (4).

A 19-month-old girl was referred to child psychiatry due to delayed speech and developmental concerns. She had no major dysmorphic features aside from a flat nasal bridge. Notable findings included exaggerated startle responses to tactile and auditory stimuli, babbling without meaningful speech, inability to follow simple commands, delayed motor milestones, and limited social interaction. Developmental assessment using the Ankara Developmental Screening Inventory (ADSI) revealed significant delays across all domains, with performance falling below the 30th percentile. The specific developmental ages and domain scores of the ADSI are presented in Figure 1. A subsequent Denver II Developmental Screening Test also confirmed significant delays across all assessed domains, including personal-social, fine motor, language, and gross motor skills.

She was born at term via cesarean section to consanguineous parents, with a birth weight of 3600 grams. There was no known family history of neurological or genetic disorders. From the neonatal period onward, she exhibited startle-like muscle contractions. Electroencephalography (EEG), magnetic resonance imaging (MRI), and biochemical test results were unremarkable. Following psychiatric and developmental evaluation, the patient was assessed in collaboration with the pediatric neurology department. Based on this joint evaluation, the neurology team referred her for genetic testing, which identified a novel homozygous c.629G>T p.(Gly210Val) variant in the *SLC6A5* gene, thereby confirming the diagnosis of hyperekplexia. Initial treatment with phenobarbital and levetiracetam was replaced with clonazepam after diagnostic confirmation, resulting in a reduction of startle episodes. Further evaluations revealed bilateral partial hearing loss and a hemodynamically insignificant secundum atrial septal defect.

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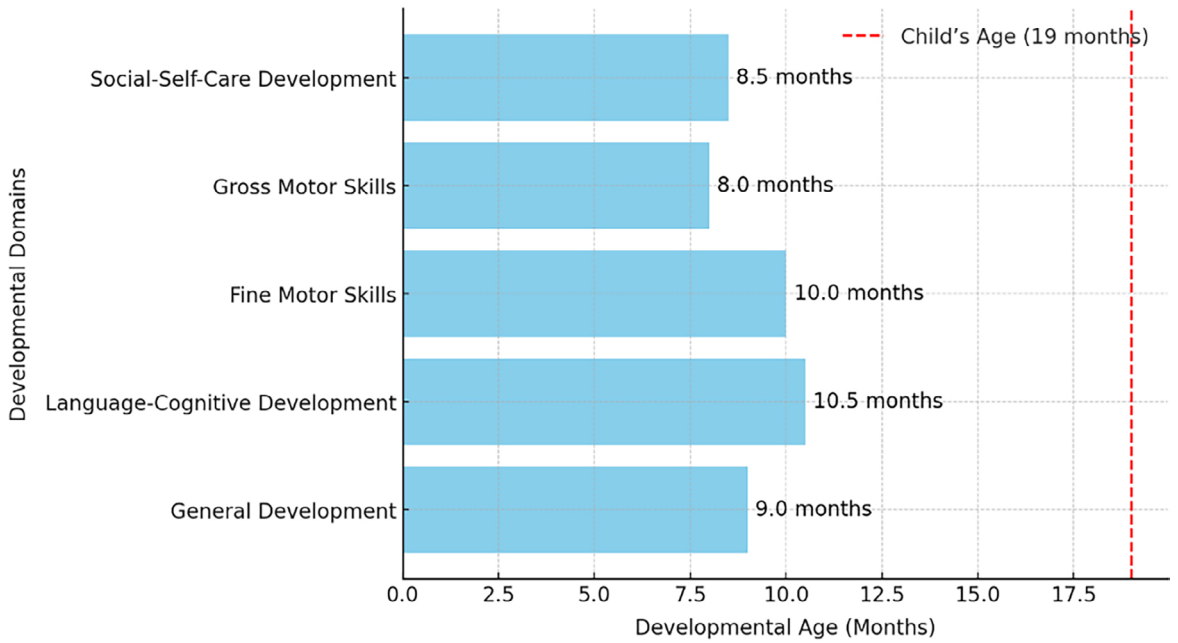

Figure 1. Developmental ages based on the Ankara Developmental Screening Inventory (ADSI) results compared to the child's chronological age (19 months).

At the time of psychiatric evaluation, the patient was diagnosed with GDD. Although she exhibited speech delay and limited social interaction, she did not meet the diagnostic criteria for autism spectrum disorder (ASD) at that stage. A multidisciplinary early intervention plan was initiated, including individualized special education, speech-language therapy, and parental psychoeducation. The parents were advised on activities to stimulate the child's development at home, promote social play, and reduce screen time. Regular psychiatric follow-up was arranged for developmental surveillance and to monitor for the possible emergence of ASD, attention-deficit/hyperactivity disorder (ADHD), ID, or other psychiatric disorders.

This case involves a previously unreported *SLC6A5* variant associated with prominent developmental delays. Although the exact pathogenicity of this variant is uncertain, the breadth of neurodevelopmental impairment suggests an effect extending beyond motor circuits to cognitive and psychiatric domains. The co-occurrence of hearing loss and an atrial septal defect may further complicate developmental outcomes. GDD and ID are among the most prevalent neurodevelopmental disorders in childhood and are associated with substantial long-term morbidity. Approximately half of GDD/ID cases are linked to genetic etiologies (5). Compared to other hyperekplexia-related genes, *SLC6A5* and *GLRB* mutations have been more frequently associated with GDD/ID, learning difficulties, and speech impairments (2, 4, 6). These associations are summarized in Table 1, which compares the impact of different hyperekplexia-related gene mutations on GDD/ID, speech delay, and learning difficulties. Such manifestations likely arise from early and diffuse disruptions in neurodevelopmental pathways (6). In particular, mutations in *SLC6A5*, which encodes the presynaptic GlyT2, disrupt glycinergic inhibitory neurotransmission. This impaired inhibition not only explains the exaggerated motor startle responses but may also affect broader neural circuits involved

Table 1: Comparison of the effects of hyperekplexia-related gene mutations on global developmental delay (GDD), intellectual disability (ID), speech delay, and learning difficulties

Gene mutation	GDD/ID	Speech delay	Learning difficulties
GLRA1	Less common	Less common	Moderate
GLRB	Common	Very common (92%)	Common
SLC6A5	Common	Common	Common

in cognition, learning, and social behavior, thereby contributing to developmental delay and psychiatric manifestations.

Although hyperekplexia is pharmacologically manageable, associated cognitive and behavioral impairments often persist (7). This underscores the critical role of child psychiatrists in both diagnostic assessment and long-term follow-up. Early multidisciplinary intervention—particularly with active family engagement—has been shown to improve prognosis (8). In this case, early referral to child psychiatry enabled timely developmental evaluation and the initiation of a tailored support program, including special education, speech-language therapy, and parental guidance. Given the high prevalence of psychiatric comorbidities such as ASD and ADHD in genetic neurodevelopmental conditions, ongoing psychiatric surveillance remains essential (9, 10).

In conclusion, this case highlights the broader neurodevelopmental implications of SLC6A5-related hyperekplexia and underscores the importance of psychiatric and developmental evaluation in genetic disorders of this kind. Comprehensive management, including early diagnosis, individualized therapies, and longitudinal follow-up, is essential to optimize developmental outcomes. Written informed consent was obtained from the patient's parents for the publication of this case report and the accompanying images.

Informed Consent: Written informed consent was obtained from the patient's parents for the publication of this case report and the accompanying images.

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