Case Report

A Confusing Coincidence: Neonatal Hypoglycemic Seizures and Hyperekplexia

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Hyperekplexia (HE), first described by Kirstein and Silfverskiold in 1958, is a rare and nonepileptic clinical entity characterized by exaggerated and generalized startle responses to acoustic, optic, or tactile stimuli [1]. Minimal stimuli can cause severe jerk-like movements in all the limbs. The symptoms of the disease can lead to unavoidable falls with no loss of consciousness that often diminish with age or continue until adulthood.

Glycine is one of the major inhibitory neurotransmitters in the central nervous system. The glycine receptors cause postsynaptic hyperpolarization and synaptic inhibition through chloride channels in brain and brain stem. The main pathologic impairment is the inability of glycine, which is one of the major inhibitory neurotransmitters in the central nervous system, to display its inhibitory effects, particularly in the brain stem [2]. Hyperekplexia is known to be genetic or sporadic with the genetic form being more frequent. Genetic studies have shown that most of the genetic cases are autosomal dominant and that the responsible gene is found in the alpha-1 and beta subunits and glycine-carrying parts of glycine receptors as well as in the proteins of gephyrin and collybistin that both have glycine-like effects [3]. The sporadic cases of HE are rare and are either idiopathic or due to factors such as encephalitis, tumors, inflammation, and disgenesis [4].

Hypoglycemia is a frequent problem in the newborn. Serious hypoglycemia can lead to optic and mental disorders, epilepsy, and brain damage. Hypoglycemia causes convulsions by increasing glutamate, the main excitatory neurotransmitter of the brain [5].

2. Case

The baby boy was born full-term by spontaneous vaginal delivery to a 28-year-old healthy female mother as a fifth pregnancy. Immediately after birth, the infant cried but displayed no change in skin color, and his Apgar scores were 7 and 9 at one and 5 minutes, respectively. There was no history of a consanguineous marriage between the parents or the presence of a similar disease in the other children of the family or other family members. At birth, his weight was 2850 grams (10–50 percentile), height was 50 cm (50 percentile), and his head circumference was 34 cm (50 percentile). In his physical examination, there was no
The most important clinical feature of hyperekplexia is extreme reaction to stimuli caused by genetic mutations or incomplete development of the inhibitory glycine receptors in the brain secondary to encephalitis, tumors, inflammation, and dysgenesis [4, 6, 7]. The clinical presentation of hyperekplexia differs with the age of the patient, and this situation leads to difficulty in diagnosis. Particularly in the newborn, the diagnosis is quite difficult because of the many manipulations in the intensive care unit, increased susceptibility to stimuli, and metabolic problems (hypoglycemia, hypocalcemia). Feeding difficulties, life-threatening pathologic apnea, sudden infant death, complete bundle branch block, and cerebral anoxia can occur in serious hyperekplexia [8].

In the differential diagnosis of hyperekplexia; paroxysmal extreme pain disorder, epilepsy, nonketotic hyperglycemia, Crisponi syndrome, and neonatal tetanus should be considered. It has been reported that in seriously affected infants, severe jerk-like spasms can be confused with epileptic attacks and even with status epilepticus. Many studies have interpreted the absence of epileptic activity on EEG during repeating jerks as being indicative of HE [8, 9]. In our case, the diagnosis of hyperekplexia was considered because convulsions continued in spite of corrected hypoglycemia, the EEG findings were normal and jerks diminished significantly with clonazepam treatment. Our hyperekplexia case was differentiated from neonatal tetanus by the fact that complaints started immediately after birth and were nonprogressive. The differentiation from paroxysmal extreme pain disorder was made because the jerks were triggered with painful stimuli as well as with acoustic and optic stimuli and no change in skin color was observed; and from Crisponi syndrome due to the lack of saliva flow during convulsions, generalized convulsions, and no other additional abnormality; and then nonketotic hyperglycaemia was excluded by the normal amino acid analysis [10].

In hypoglycemia, the main excitatory amino acid glutamate is poorly reabsorbed due to its extreme secretion in the synaptic area and insufficiency of energy-dependent channels and thus leads to increased amounts of secondary extracellular glutamate which in turn induces convulsions [11]. In the neonatal period, the receptors for glutamate (particularly N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA)) are well developed, while the inhibitory system is still weak [11, 12]. Glycine acts as an inhibitor in the central nervous system and at the same time functions as an excitatory coagonist [13]. Animal studies have shown that a genetic or experimental defect in glycine receptors increase the susceptibility of NMDA receptors; this high susceptibility and defective inhibitory mechanism leads to extreme stimulation of the excitatory activity and so to uncontrolled seizures and convulsions [14, 15]. Hyperekplexia is primarily caused by a genetic defect in glycine receptors; rarely it can also occur secondary to encephalitis, tumors, inflammation, and dysgenesis. Our patient was a primary case of hyperekplexia, but the initial convulsions secondary to hypoglycemia caused difficulty in diagnosis. The increase in glutamate due to hypoglycemia plus the glycine defect causing hyperekplexia might have significantly increased cortical irritation and thus the hyperplexia, leading to a status epilepticus-like clinical presentation. Further well-designed studies on the relationship between hyperekplexia and hypoglycemia are required.

Although hyperekplexia is a rare nonepileptic phenomenon, it should be considered in cases of convulsions resistant to therapy, in convulsions with no organic underlying disease or in persistent convulsion-like involuntary movements after treatment of the underlying disease. With
a correct diagnosis of hyperekplexia, unnecessary antiepileptic therapy and possible side effects can be avoided and appropriate treatment can diminish convulsion attacks.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] L. Kirstein and B. P. Silfverskiold, "A family with emotionally precipitated drop seizures," Acta psychiatrica et neurologica Scandinavica, vol. 33, no. 4, pp. 471–476, 1958.

[2] M. Z. Seidahmed, M. A. Salih, O. B. Abdulbasit et al., "A novel syndrome of lethal familial hyperekplexia associated with brain malformation," BMC Neurology, vol. 12, article 125, 2012.

[3] R. J. Harvey, M. Topf, K. Harvey, and M. I. Rees, "The genetics of hyperekplexia: more than startle!," Trends in Genetics, vol. 24, no. 9, pp. 439–447, 2008.

[4] J. S. Goraya, D. Shah, and B. Poddar, "Hyperekplexia in a girl with posterior fossa malformations," Journal of Child Neurology, vol. 17, no. 2, pp. 147–149, 2002.

[5] E. W. Y. Tam, L. A. Haeusslein, S. L. Bonifacio et al., "Hypoglycemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in neonates at risk for encephalopathy," Journal of Pediatrics, vol. 161, pp. 88–93, 2012.

[6] K. Ruprecht, M. Warmuth-Metz, W. Waespe, and R. Gold, "Symptomatic hyperekplexia in a patient with multiple sclerosis," Neurology, vol. 58, no. 3, pp. 503–504, 2002.

[7] V. Praveen, S. K. Patole, P. Ryan, and J. S. Whitehall, "Unusual presentation of cerebral dysgenesis in a neonate," International Pediatrics, vol. 17, no. 3, pp. 164–165, 2002.

[8] E. Shahar and R. Raviv, "Sporadic major hyperekplexia in neonates and infants: clinical manifestations and outcome," Pediatric Neurology, vol. 31, no. 1, pp. 30–34, 2004.

[9] R. J. Leventer, I. J. Hopkins, and L. K. Shield, "Hyperekplexia as cause of abnormal intrauterine movements," The Lancet, vol. 345, no. 8947, p. 461, 1995.

[10] J. S. Davies, S. K. Chung, R. H. Thomas et al., "The glycinergetic system in human startle disease: a genetic screening approach," Frontiers in Molecular Neuroscience, vol. 3, article 8, 2010.

[11] F. S. Silverstein and F. E. Jensen, "Neonatal seizures," Annals of Neurology, vol. 62, no. 2, pp. 112–120, 2007.

[12] R. M. Sanchez and F. E. Jensen, "Modeling hypoxia-induced seizures and hypoxic encephalopathy in the neonatal period," in Models of Seizures and Epilepsy, A. Pitanken, P. A. Schwartzkroin, and S. L. Moshe, Eds., Elsevier, San Diego, Calif, USA, 2006.

[13] E. J. Wiltshire, N. K. Poplawski, J. R. Harrison, and J. M. Fletcher, "Treatment of late-onset nonketotic hyperglycinaemia: effectiveness of imipramine and benzoate," Journal of Inherited Metabolic Disease, vol. 23, no. 1, pp. 15–21, 2000.

[14] H. Möhler, D. Boison, P. Singer, J. Feldon, M. Pauly-Evers, and B. K. Yee, "Glycine transporter I as a potential therapeutic target for schizophrenia-related symptoms: evidence from genetically modified mouse models and pharmacological inhibition," Biochemical Pharmacology, vol. 81, no. 9, pp. 1065–1077, 2011.

[15] B. K. Yee, E. Balic, P. Singer et al., "Disruption of glycine transporter I restricted to forebrain neurons is associated with a procognitive and antipsychotic phenotypic profile," Journal of Neuroscience, vol. 26, no. 12, pp. 3169–3181, 2006.