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Hyperekplexia is a Rare Disorder in Newborn Infants

Bharti D* and Adcock BJ

Department of Pediatrics, East Tennessee State University, USA

***Corresponding author:** Des Bharti, Professor, Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee 37614, USA, Tel: 423-439-6222; Fax: 423-439-8066; Email: bharti@etsu.edu

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Abstract

Hyperekplexia is an uncommon disorder in newborn infants. We are reporting a neonate with hyperekplexia who presented with exaggerated startle reaction, major episodes of apnea and stiffness of extremities immediately after birth.

Keywords: Hypertonicity; Bradycardia; Hyperekplexia

Abbreviations: EMG: Electromyography; PDE: Pyridoxine-Dependent Epilepsy.

Case Presentation

3755 grams, full-term male infant was born by a repeat cesarean section at 39 weeks gestation to a 28-year-old, gravida 3 para 2012. She previously had a full-term female infant and one ectopic pregnancy. Apgar's of 4, 7, and 8 at 1, 5 and 10 minutes. Maternal history is remarkable for a history of petite mal seizures as a child. She claims to have outgrown the seizures by 11 years of age. She also has a history of migraines. Her prenatal labs were unremarkable. She has had a history of HPV infection. She denied history of smoking, drug abuse or alcohol intake. Pregnancy was otherwise uncomplicated. The older sibling of the infant did not have any respiratory or neurological problems at birth. She has had normal growth and development.

The infant was born hypoactive with no spontaneous breathing. He required positive pressure ventilation via face mask. As the infant was stimulated in the delivery room, he was noted to have hypertonicity of the upper and lower extremities with the arms outstretched and in a flexed tonic position for several seconds to minutes. No jerking or colonic movements were noted. Infant's overall exam was unremarkable and no dysmorphology was noted. The infant had an exaggerated startle on admission to the newborn nursery. He was noted to have several episodes of prolonged apnea with associated desaturation and bradycardia. A simple tap on the infant's knee led to stiffness of all four extremities with associated prolonged apnea, bradycardia and desaturation. The mother attempted to nipple feed the infant, but he was not making any efforts to suckle. He was transferred to a level three neonatal intensive care unit on nasal cannula 2 liters per minute, 21% FiO_2.

Upon arrival to the NICU, the infant was noted to have several episodes of stiffness of all four extremities, bilateral clonus, hypertonicity with associated apnea, bradycardia and oxygen desaturation. During these episodes, the infant required positive pressure ventilation for several minutes. Septic evaluation was negative. Pediatric neurology was consulted, and EEG did not reveal any seizure activity. A non-contrast MRI of the brain was reported normal. The infant was started on oral clonazepam at 0.01 mg/kg twice a day. The dose was gradually increased to 0.02 mg/kg twice a day. The apnea subsided, and the infant was weaned off supplemental FiO_2 within 48 hours. Serum amino acid and urine organic acid were reported in normal range. Pyruvate level was within the normal range. Once stabilized on clonazepam, he was able to nipple feed the adequate volumes. Prior to discharge, the infant was not having any spontaneous episodes of startle response, bradycardia or apneas for over five days.

The infant was discharged from the NICU after 11 days on clonazepam 0.02 mg/kg twice a day with a recommendation to have follow-up by the primary care provider and pediatric neurologist. Molecular studies showed a pathogenic variant: c.634C>T (p.Arg212) and a likely pathogenic variant: c.297+1G>T (splice donor) of the GLRB gene, consistent with a diagnosis of autosomal recessive hyperekplexia type 2 (HKPX2).

The infant required inpatient hospitalization around one month of age for mild respiratory distress manifesting as chest retractions. He was subsequently diagnosed with severe gastroesophageal reflux disease and tracheomalacia. The infant underwent gastrostomy tube placement and fundoplication at five months of age due to failure to thrive, significant feeding aversion and gastroesophageal reflux disease.

Discussion

Hyperekplexia also called a startle disease or congenital stiff-man syndrome is a rare non-seizure disorder that typically presents with exaggerated persistent startle reaction in the newborn period [1-4]. The classic presentation is a tight closure of eyes, partially flexed arms are held over the head with flexed neck, trunk, hips and knees. These episodes can be triggered by a loud sound, touch, or a visual stimulus. The muscular stiffness and the myoclonus are major presenting features. The infant may have stiffness with clinching of fists and crowing of toes and a staring spell. The condition is non-fatigable and startle response can be repeatedly elicited by tapping the glabella [5]. This disorder is usually familial, mostly presenting as autosomal dominant disorder. It may present in the neonatal period or late childhood. The tonic spasms may appear as generalized tonic seizure disorders leading to apnea with a potential for death, if not diagnosed and managed early. Some of the infants could present with muscle twitching while falling asleep, so called hypnogogic myoclonus. Some infants have been reported to show recurrent seizures. Potentially, these infants may present as sudden infant death syndrome. Generally, most infants have steady improvement by one year of age. Occasionally, older individuals with hyperekplexia may startle with loud noise and potentially can sustain fall. Exact etiology of the disorder is not clearly known. The proposed pathways are hyperactive cortical neurons, disordered inhibition pathways of the brain, and abnormal serotonin pathways. Some adult patients have been reported to have pontine or posterior thalamic infarcts. Central apneas may be related to brainstem dysfunction and feeding difficulties with ensuing aspiration and respiratory spasms may lead to sudden infant death syndrome. Majority of the patients have a normal intelligence and appropriate neurological outcome [6].

Electroencephalography may be normal, or it could possibly show spike-wave activity initially during tonic spasticity followed by slowing of the background activity with eventual flattening attributed to significant apnea, bradycardia with hypoxemia [7]. A simple flexion of the head and legs towards the trunk could be life-saving when major stiffness impedes breathing. No specific findings have been reported on CT scan or MRI of the head. Majority of the cases of hyperekplexia are associated with mutation in the GLRA 1 gene. This gene provides instruction for making alpha-1 subunit of the glycine receptor protein. Normally, this protein attaches to glycine and prevents signaling between neuronal cells. Glycine acts as an important neurotransmitter. GLRA 1 gene mutation leads to abnormal production of the receptor that does not respond to glycine. This leads to dysregulation of signals in the spinal cord and brainstem. Both autosomal dominant and recessive patterns have been reported with hereditary hyperekplexia. Another gene abnormality may be related to mutation of SLC6A5 or GLRB gene. The mother of our index infant reported petite mal seizures as a child. She claims that these episodes subsided by 11 years of age. These so called petite mal seizures could have been a presentation of hyperekplexia. Both parents were instructed to have an appointment with a geneticist for gene analysis. Our patient continued to have feeding problems, failure to thrive and associated gastro-esophageal reflux disease.

Hyperekplexia was first described in 1958 by Kirstein and Silverskoild [8]. Subsequently several additional cases are reported in the literature. Electromyography (EMG) may be a helpful diagnostic tool. It shows a typical permanent muscular activity with periods of electrical silence. EMG may be used to monitor improvement and progression in minor instances of hyperekplexia. Nerve conduction velocity is reported normal. This disorder needs to be differentiated from jitteriness, neonatal abstinence syndrome, benign myoclonus, benign familial seizures, pyridoxine deficiency seizures, early myoclonic encephalopathy, neonatal tetanus, neonatal botulism, phenothiazine toxicity or cerebral palsy.

Jitteriness is a common occurrence in neonates [9]. It is a low frequency, large amplitude spontaneous or provoked movement not associated with eye movements or gaze abnormality. They may be associated with exaggerated deep tendon reflexes and clonus. Jitteriness can be easily suppressed by examiner after holding the extremities. It is seen in 40% of healthy infants. Jitteriness can be associated perinatal asphyxia, neonatal abstinence syndrome, hypoxic encephalopathy, hypocalcemia and hypoglycemia. Neonatal abstinence syndrome from opiate, cocaine or amphetamine exposure can manifest with hypertonicity, sleep abnormality, tremors, and excessive cry [10]. Opiate withdrawal may require morphine, phenobarbital or buprenorphine therapy.

Some infants may have seizures following maternal exposure of drugs.

Neonates may have benign myoclonus presenting as sudden, brief contraction of a group of muscles. These are not associated with EEG abnormality [11]. They are reported in non-rapid eye movement sleep and generally disappear during wakeful state. The neurological exam is unremarkable. They end by third month of life. Fifth day fit is an entity that presents in otherwise healthy newborn infant at the end of the first week with multiple focal clonic activities lasting less than two weeks. This has normal outcome but occasionally some infants may require antiseizure medications for status epilepticus.

Pyridoxine deficiency related seizures [12] are typically generalized tonic-clonic, although myoclonic seizures or infantile spasms have been described. All children younger than 3 years with early onset intractable seizures or status epilepticus should be considered for a trial of pyridoxine. Pyridoxine-dependent epilepsy (PDE) was first described in 1954. The ALDH7A1 gene mutations resulting in α-aminoadipic semialdehyde dehydrogenase deficiency, as a cause of PDE, was reported in 2005. Over 100 cases have been reported. PDE is a rare autosomal recessive disorder causing intractable seizures in neonates and infants. Seizures in these patients are typically resistant to anti-epileptic treatment but respond dramatically to the administration of pyridoxine. Benign Familial Neonatal convulsions is an autosomal dominant condition that presents with focal or multi-focal tonic or clonic activity, a family history of seizures and no other neurological problem [13]. The seizures resolve completely and interictal EEG is normal. EBN1 type is associated with mutation in voltage-gated potassium channel KCNQ2 and EBNQ2 is associated with partial deletion of chromosome 8q24. Early myoclonic encephalopathy noted in early neonatal period has unknown etiology. It has been reported with non-ketotic hyperglycemia, D-glycemic acidemia, methyl malonic acidemia and carbamyl phosphate synthetase associated hyperammonemia. EEG shows typical burst suppression pattern. Infants exhibit developmental delays, hypotonic and microcephaly from cerebral atrophy. The initial myoclonus resolves but they develop intractable seizures refractory to medications. The drug of choice for hyperekplexia is clonazepam, a gamma amino butyric acid receptor agonist. The degree of hypertonicity may not be significantly altered by clonazepam. Forced flexion of the head and legs towards the belly could ameliorate the prolonged stiffness. In infants who develop epilepsy, there may be a need to treat with phenobarbital, levetiracetam, and phenytoin or sodium valproate. Spontaneous resolution has been reported with increasing age and some infants may have delayed gross motor development [14].

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