Hyperekplexia or Epilepsy? A Diagnostic Challenge in Infantile Apneic Events

Dr Nithya S Cherian[1], Dr Rupanagudi Tanvi, Dr Palle Nikitha
[1]*Junior Resident, Department of Paediatrics, Jawaharlal Nehru Medical college Belgavi*

Abstract:-Background -Hyperekplexia is an often underrecognized motor disorder in infants that closely resembles epilepsy. It is characterized by recurrent and exaggerated startle responses, along with brief episodes of intense, generalized muscle stiffness (hypertonia) triggered by sudden auditory or tactile stimuli, often occurring from birth.

Case presentation – A 4-month-old male infant presented with abnormal movements of the upper and lower limbs, associated with bluish discoloration of the face, lips, and body. These episodes occurred approximately 5-6 times per day, each lasting less than 2 minutes. The child also exhibited a history of exaggerated startle reflex. There was no improvement in the episodes following treatment with anti-seizure medications, including levetiracetam. However, a noticeable decrease in the frequency of episodes was observed after the initiation of clonazepam.

Conclusion – This case report underscores the importance of considering hyperekplexia in the differential diagnosis of unexplained abnormal movements in infants and highlights the potential therapeutic role of clonazepam in managing this condition. Further investigation into the underlying genetic or neurophysiological mechanisms of hyperekplexia may enhance diagnostic and treatment approaches.

INTRODUCTION

Hyperekplexia, or startle disease, is a rare neurological disorder that is not epileptic in nature. It is marked by an exaggerated and persistent startle reflex triggered by unexpected auditory, visual, or somatosensory stimuli, along with generalized muscle stiffness and nocturnal myoclonus.This condition is primarily caused by a genetic mutation, often involving the arginine residue at position 271. This mutation disrupts glycinergic inhibition, leading to neuronal hyperexcitability. Hyperekplexia is usually inherited in an autosomal dominant manner, showing complete penetrance but varying in its expression.Symptoms can emerge as early as fetal development, appearing as unusual intrauterine movements, or at any stage from birth to adulthood. In infants, the disorder often presents as an exaggerated startle response, prolonged muscle spasms, a characteristic fetal-like posture with clenched fists, and a distinct anxious stare. In severe cases, the spasms can mimic generalized tonic seizures, potentially leading to apnea and even fatal outcomes.A definitive clinical sign of hyperekplexia is the persistent generalized flexor spasm triggered by tapping the nasal bridge, which does not diminish with repeated stimulation.

CASE PRESENTATION

A 4-month-old male infant, born to non-consanguineous parents (third-degree relatives), presented with tonic seizures associated with apneic episodes and cyanosis, occurring 5-6 times per day. The child also had a history of exaggerated startle responses. The antenatal history was unremarkable; however, postnatally, he required NICU admission due to birth asphyxia and respiratory distress syndrome (RDS). At three months of age, he was evaluated at a local hospital for convulsions and was started on oral levetiracetam. A cranial ultrasound (USG) at that time showed periventricular and supraventricular changes. While there was initial improvement with levetiracetam, the frequency of episodes increased over the past 10 days before presentation. On examination, the child had stable vitals, normal anthropometry, and no dysmorphic features. Neurologically, muscle tone was normal with brisk reflexes, and the nasal tap test was positive, indicating a generalized flexor spasm without habituation. Further investigations, including EEG and cardiac evaluation, were normal, but blood tests revealed nutritional iron deficiency anemia. Based on clinical findings, a provisional diagnosis of Hyperekplexia was made, and whole exome sequencing was advised for genetic confirmation. Levetiracetam was discontinued, and the child was started on clonazepam, leading to a significant reduction in episode frequency, with no fresh episodes observed for 36 hours before discharge.

DISCUSSION

Hyperekplexia is a rare hereditary neurological disorder characterized by an exaggerated startle reflex, generalized muscle rigidity, and episodic tonic spasms, which can mimic epileptic seizures. It is most commonly caused by mutations in genes associated with glycinergic neurotransmission, such as GLRA1, leading to impaired inhibitory signaling and neuronal hyperexcitability. The condition can manifest from fetal life to adulthood, with neonatal-onset cases often presenting with excessive startle responses, apnea, and stiffness, which can lead to life-threatening events if misdiagnosed as epilepsy or other seizure disorders. A key clinical sign of hyperekplexia is the persistent startle response to tactile or auditory stimuli, with a positive nasal tap test—an important bedside diagnostic tool. In contrast to epilepsy, EEG findings are typically normal, reinforcing the need for a high index of suspicion in cases of recurrent tonic spasms and apnea in neonates or infants.

Early diagnosis is crucial as hyperekplexia is highly responsive to benzodiazepines such as clonazepam, which enhances GABAergic inhibition and reduces excessive startle responses. Delayed or incorrect diagnosis can lead to unnecessary use of antiepileptic drugs, which may not effectively control symptoms. In this case, initial treatment with levetiracetam provided partial relief but was ultimately ineffective, necessitating a switch to clonazepam, which resulted in rapid symptom resolution. Whole exome sequencing was advised for genetic confirmation, as identifying causative mutations can guide management and provide valuable information for genetic counseling. This case underscores the importance of recognizing hyperekplexia as a differential diagnosis in infants with recurrent tonic spasms, apnea, and exaggerated startle reflexes, emphasizing the role of targeted therapy in preventing potential life-threatening complications.

Sudden infant death syndrome (SIDS) has been widely documented in cases of hyperekplexia. Central apnea, resulting from brainstem dysfunction, or peripheral apnea due to feeding difficulties leading to aspiration and respiratory muscle spasms, are considered potential mechanisms underlying SIDS. Interestingly, these apneic episodes have been observed to resolve spontaneously by the age of two years. Additionally, sudden death in hyperekplexia may also be linked to complete heart block and apnea occurring during seizure-like episodes.

CONCLUSION

Hyperekplexia is often misdiagnosed as epilepsy and is frequently treated with multiple antiseizure medications. However, recognizing the condition becomes straightforward with prior awareness of the disease. A hallmark feature of hyperekplexia is the exaggerated startle response, which can be reliably triggered by tapping the nasal bridge, making it a crucial component of the clinical examination for suspected cases. In most patients, routine investigations such as serum electrolyte levels, neuroimaging, EEG, and other biochemical tests yield normal results. However, video-EEG or an EEG conducted with simultaneous observation by an experienced technician can aid in distinguishing hyperekplexia from epileptic seizures. Episodes of hypertonicity accompanied by cyanosis can often be alleviated using the Vigevano maneuver, a simple technique involving the flexion of the head and legs toward the trunk.

REFERENCES

[1] Wang CH, Hernandez CC, Wu J, et al.: A missense mutation A384P associated with human hyperekplexia reveals a desensitization site of glycine receptors. J Neurosci. 2018, 38:2818-31. 10.1523/JNEUROSCI.0674-16.2018

[2] Sprovieri T, Ungaro C, Sivo S, et al.: Clinical features and genetic analysis of two siblings with startle disease in an Italian family: a case report. BMC Med Genet. 2019, 20:40. 10.1186/s12881-019-0779-x

[3] Koning-Tijssen MA, Brouwer OF: Hyperekplexia in the first year of life . Mov Disord. 2000, 15:1293-6. 10.1002/1531-8257(200011)15:6<1293::aid-mds1047>3.0.co;2-k

[4] Chen CH, Lee HF, Chi CS: Hyperekplexia (startle disease) mimicking neonatal seizures: report of one case. Acta Paediatr Taiwan. 2007, 48:20-2.

[5] Zhan FX, Wang SG, Cao L: Advances in hyperekplexia and other startle syndromes . Neurol Sci. 2021, 42:4095-107. 10.1007/s10072-021-05493-8

[6] Bode A, Lynch JW: The impact of human hyperekplexia mutations on glycine receptor structure and function. Mol Brain. 2014, 7:2. 10.1186/1756-6606-7-2

[7] Harvey RJ, Topf M, Harvey K, Rees MI: The genetics of hyperekplexia: more than startle! . Trends Genet. 2008, 24:439-47. 10.1016/j.tig.2008.06.005

[8] McMaster P, Cadzow S, Vince J, Appleton B: Hyperekplexia: a rare differential of neonatal fits described in a developing country. Ann Trop Paediatr. 1999, 19:345-8. 10.1080/02724939992185

[9] Praveen V, Patole SK, Whitehall JS: Hyperekplexia in neonates. Postgrad Med J. 2001, 77:570-2. 10.1136/pmj.77.911.570

[10] Agarwalla SK, Patro D, Ali N, Pattanaik A: Hyperekplexia in a neonate: a seizure mimicker . Int J Res Med Sci. 2018, 6:375-7. 10.18203/2320-6012.ijrms20175755

[11] Horváth E, Farkas K, Herczegfalvi A, Nagy N, Széll M: Identification of a novel missense GLRA1 gene mutation in hyperekplexia: a case report. J Med Case Rep. 2014, 8:233. 10.1186/1752-1947-8-233

[12] Mine J, Taketani T, Yoshida K, et al.: Clinical and genetic investigation of 17 Japanese patients with hyperekplexia. Dev Med Child Neurol. 2015, 57:372-7. 10.1111/dmcn.12617

[13] Vigevano F, Di Capua M, Dalla-Bernardina B: Startle disease: an avoidable cause of sudden infant death .Lancet. 1989, 1:216. 10.1016/s0140-6736(89)91226-9

[14] Zhou L, Chillag KL, Nigro MA: Hyperekplexia: a treatable neurogenetic disease . Brain Dev. 2002, 24:669-74. 10.1016/s0387-7604(02)00095-5