RESEARCH PAPER

Neonatal Hyperekplexia Mimicking Epileptic Seizures: A Diagnostic Pitfall in Early Infancy

Running Title: Neonatal hyperekplexia mimicking seizures

Sunil Reddy Bana[1], Bhavana Koppad[2*], Harsha Vardhan[3]

[1] Junior Resident, Department of Paediatrics, KLE Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, Karnataka, India.

[2*] Professor, Department of Paediatrics, KLE Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, Karnataka, India. (Corresponding Author) Email: bhavna.d23@gmail.com, Phone: +91-9986157763

[3] Junior Resident, Department of Paediatrics, KLE Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, Karnataka, India.

Received: 20th Feb, 2026 | **Revised:** 4th Mar, 2026 | **Accepted:** 25th Mar, 2026 | **Available Online:** 10th Apr, 2026

ABSTRACT

Background: Hyperekplexia is a rare neonatal neurogenetic disorder caused by impaired glycinergic inhibitory neurotransmission, most commonly due to pathogenic variants in the GLRA1 gene. In early infancy, it frequently masquerades as epileptic seizures, resulting in misdiagnosis and unnecessary antiseizure treatment.

Case Presentation: We report a neonate who presented with recurrent stimulus-induced episodes of generalized tonic stiffening beginning soon after birth. The events were consistently precipitated by tactile or auditory stimuli and occurred with preserved consciousness. Interictal neurological examination and electroencephalography were normal. A reproducible exaggerated startle response elicited by the bedside nose-tap test strongly suggested hyperekplexia.

Outcome: Whole-exome sequencing identified a homozygous missense variant in exon 6 of the GLRA1 gene (c.697G>C; p.Gly233Arg), classified as a variant of uncertain significance, with strong in-silico pathogenicity predictions and phenotypic concordance in the setting of parental consanguinity. Initiation of clonazepam led to rapid and sustained clinical improvement.

Conclusion: Early bedside examination with molecular genetic testing to accurately diagnose hyperekplexia and emphasizes the importance of early recognition of this treatable seizure mimicker in neonates.

Keywords: Hyperekplexia; Neonate; Startle response; GLRA1 gene; Clonazepam; Seizure mimicker; Nose-tap test; Glycinergic neurotransmission.

How to cite this article: Bana SR, Koppad B, Vardhan H. Neonatal Hyperekplexia Mimicking Epileptic Seizures: A Diagnostic Pitfall in Early Infancy. Int J Drug Deliv Technol. 2026;16(29s):713-715. DOI: 10.25258/ijddt.16.29s.90

Source of support: Nil.

Conflict of interest: The authors declare no conflict of interest.

INTRODUCTION

Hyperekplexia is a rare inherited neurogenetic disorder characterized by dysfunction of glycinergic inhibitory neurotransmission in the brainstem and spinal cord, resulting in neuronal hyperexcitability and exaggerated startle responses. Glycine functions as the principal inhibitory neurotransmitter in these regions, and impairment of glycine receptor function leads to excessive motor responses to trivial sensory stimuli. The estimated prevalence is less than 1 per 1,000,000 live births, although the condition is likely underdiagnosed due to frequent misinterpretation as epilepsy. [1–3]

Clinically, hyperekplexia presents in the neonatal period or early infancy with exaggerated, non-habituating startle responses triggered by auditory, tactile, or visual stimuli, followed by transient generalized hypertonia. These episodes may be associated with apnea, cyanosis, and feeding difficulties, potentially resulting in life-threatening complications if not recognized promptly. [1,2,4]

A key distinguishing feature is the reproducibility of the exaggerated startle response using bedside maneuvers such as tapping the nasal bridge (nose-tap test), which helps differentiate hyperekplexia from epileptic seizures. Unlike epilepsy, affected infants

typically maintain preserved consciousness and demonstrate normal electroencephalography. [2,4]

Hyperekplexia demonstrates significant genetic heterogeneity, with pathogenic variants identified in multiple genes involved in glycinergic neurotransmission, including GLRA1, GLRB, SLC6A5, GPHN, and ARHGEF9. Mutations in GLRA1, which encodes the alpha-1 subunit of the glycine receptor, represent the most common genetic cause and may exhibit autosomal dominant or autosomal recessive inheritance patterns. [1,3] Early recognition is essential because hyperekplexia is highly responsive to treatment with clonazepam, which enhances inhibitory neurotransmission and results in rapid and sustained symptom improvement. [1,5]

Timely diagnosis prevents unnecessary antiseizure therapy, reduces morbidity, and significantly improves clinical outcomes in affected infants. [1]

CASE PRESENTATION

A four-month-old male infant, born at term to third-degree consanguineous parents, presented with recurrent episodes of sudden generalized stiffening of all four limbs. These episodes began on the second day of life, lasted approximately two to three minutes, and occurred five to six times daily. Events were consistently triggered by minimal tactile or auditory stimuli and occurred with preserved consciousness.

The infant was delivered vaginally with a birth weight of 3 kg. He did not cry immediately after birth and required neonatal intensive care unit admission for 14 days due to respiratory distress and feeding difficulty. During this period, the episodes of generalized stiffening were suspected to represent neonatal seizures, and the infant was empirically treated with antiseizure medications. Despite therapy, the episodes persisted and gradually increased in frequency over the subsequent months.

At four months of age, the mother reported repetitive tonic stiffening associated with exaggerated startle responses and transient cyanosis, without loss of consciousness. There was no history of fever, eye deviation, clonic movements, or autonomic instability during the events. No family history of similar illness or unexplained infant deaths was reported.

On examination, the infant was alert and interactive. Vital parameters were stable and no dysmorphic features were noted. Neurological examination revealed normal baseline tone, brisk deep tendon reflexes, preserved awareness during events, and a clearly positive nose-tap test that reliably reproduced an exaggerated startle response followed by generalized tonic stiffening. The remainder of the systemic examination was unremarkable.

Laboratory evaluation showed haemoglobin of 9 g/dL, suggestive of nutritional iron deficiency. Serum electrolytes, including calcium and magnesium, were within normal limits. Interictal electroencephalography showed no epileptiform discharges. Cranial ultrasonography and screening echocardiography showed no structural abnormalities. Based on the classical clinical phenotype, stimulus-induced tonic stiffening, preserved consciousness, reproducible exaggerated startle response, and normal electroencephalography, a diagnosis of hyperekplexia was considered. Clonazepam was initiated at a dose of 0.1 mg/kg/day. Within 36–72 hours, there was a marked reduction in the frequency and severity of episodes, with complete resolution of cyanotic spells.

Whole-exome sequencing identified a homozygous missense variant in exon 6 of the GLRA1 gene (c.697G>C; p.Gly233Arg). Although classified as a variant of uncertain significance, the variant demonstrated strong in-silico pathogenicity predictions (CADD score 34; REVEL score 0.916) and was highly concordant with the clinical phenotype in the context of parental consanguinity.

Parents were educated regarding the Vigevano manoeuvre (forced flexion of the head and lower limbs during an episode). At one-month follow-up, the infant remained clinically stable, with only occasional mild startle responses, improved feeding, appropriate weight gain, and no evidence of developmental delay.

DISCUSSION

Hyperekplexia is a neurogenetic disorder caused by dysfunction of glycinergic inhibitory neurotransmission in the brainstem and spinal cord. Glycine serves as the primary inhibitory neurotransmitter in these regions, and impairment of glycine receptor function results in neuronal hyperexcitability and exaggerated startle responses.[1–3]

Mutations in the GLRA1 gene represent the most common genetic cause of hyperekplexia. GLRA1 encodes the alpha-1 subunit of the glycine receptor, which plays a critical role in inhibitory neurotransmission. Both autosomal dominant and autosomal recessive inheritance patterns have been described, particularly in consanguineous families.[1,3,4]

Clinically, hyperekplexia typically presents in the neonatal period or early infancy with exaggerated, stimulus-induced startle responses followed by transient generalized hypertonia. These episodes may

be associated with apnea, cyanosis, and feeding difficulties, and in severe cases may result in life-threatening events.[1,2] Early recognition is essential because the condition may be misdiagnosed as epilepsy, leading to unnecessary investigations and inappropriate antiseizure therapy.[2]

Several clinical features help distinguish hyperekplexia from epileptic seizures. Unlike epilepsy, hyperekplexia is characterized by stimulus sensitivity, preserved consciousness, normal electroencephalography, and reproducibility of symptoms with bedside maneuvers such as the nose-tap test.[2,4] Recognition of these distinguishing features is critical for early diagnosis and appropriate management.

Clonazepam is the treatment of choice and is highly effective in reducing startle responses and improving clinical outcomes. Its therapeutic effect is mediated through enhancement of inhibitory neurotransmission. Most affected infants demonstrate rapid and sustained improvement following initiation of therapy.[1,5] Early diagnosis and treatment significantly reduce morbidity and prevent life-threatening complications such as apnea and sudden infant death. [1]

CONCLUSION

This case highlights hyperekplexia as an important and treatable seizure mimicker in early infancy. Hyperekplexia should be considered in neonates and young infants presenting with stimulus-induced tonic stiffening and preserved consciousness, particularly when electroencephalography is normal. Careful clinical evaluation, recognition of characteristic bedside signs such as the nose-tap test, and timely initiation of clonazepam can rapidly reverse symptoms and prevent unnecessary investigations and prolonged antiseizure therapy. Early recognition ensures excellent clinical outcomes, as symptoms often attenuate with age and timely therapy prevents disease related morbidity.

LIST OF ABBREVIATIONS

EEG – Electroencephalography
NICU – Neonatal Intensive Care Unit
GLRA1 – Glycine Receptor Alpha-1

PATIENT CONSENT

Written informed consent was obtained from the patient's parents for publication of clinical details and accompanying videos

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We sincerely thank the patient's family for granting consent to share clinical details for academic and scientific purposes.

REFERENCES

1. Thomas RH, Chung SK, Wood SE, et al. Hyperekplexia. GeneReviews®. University of Washington, Seattle; Updated 2024.
2. Bakker MJ, Tijssen MAJ, van Dijk JG. Startle syndromes: diagnostic and therapeutic approach. Nat Rev Neurol. 2020;16(9):479-492.
3. Burgess RW, et al. Glycinergic dysfunction in hyperekplexia. Front Mol Neurosci. 2022;15:853284.
4. Willaert RK, et al. Hyperekplexia: clinical spectrum, genetic heterogeneity, and diagnostic challenges. Orphanet J Rare Dis. 2020;15:320.
5. Carta E, et al. Clinical variability and treatment outcomes of hyperekplexia in infants. Pediatr Neurol. 2021;118:1-8.

FIGURE LEGENDS

Supplementary Figure S1. Whole exome sequencing report demonstrating a pathogenic variant in the GLRA1 gene associated with hyperekplexia.

VIDEO LEGENDS

Video 1. Nose-tap test demonstrating exaggerated startle response followed by generalized tonic stiffening with preserved consciousness.
Video 2. Stimulus-induced generalized stiffening in the infant, consistent with hyperekplexia.