Hyperekplexia Secondary to Novel SLC6A5 Homozygous Deletion Masquerading as Neonatal Seizures

Mahesh Chikkannaiah,[1,2] Laura D. Fonseca,[1] Grant Turek, [1,2] Samuel Dzodzomenyo, [1,2] Gogi Kumar [1,2]

[1]Department of Neurology, Dayton Children's Hospital, Dayton, OH

[2]Department of Pediatrics, Wright State University Boonshoft School of Medicine, Dayton, OH

INTRODUCTION

- Hyperekplexia (HPX) also known as stiff baby syndrome or startle disease is a rare genetic disease.
- It is characterized by episodes of generalized stiffness (hypertonia or tonic spasms), nocturnal myoclonus, and an exaggerated myoclonic startle reflex.[1]
- Episodes of hypertonia or tonic spasms can occur upon awakening or in response to auditory/tactile/sensory stimuli, strong emotion or stress. They gradually improve and resolve as the child grows.
- The tonic spasms can interfere with breathing and result in hypoxic brain injury or death in severe cases.[2,3]
- The startle response may persist throughout the life.
- It can be hereditary or sporadic and has been associated with a variety of gene mutations affecting the glycine receptor (Table 1).[4]

CASE SUMMARY

- A 1-day old newborn baby boy was consulted by NICU for seizure activity. Baby was born at 37+1 weeks via normal vaginal delivery. No pregnancy or delivery complications noted. APGAR scores were 8 and 9.
- Initial work up included CSF evaluation and head CT which were negative. Genetic epilepsy panel was ordered.
- Clinically, events consisted of rhythmic, generalized upper and lower extremity stiffening and clonic activity associated with cyanosis and desaturation. The events appeared atypical given generalized motor activity as opposed to focal activity, which is more common for neonatal seizures.
- The events were captured on continuous video EEG with initial EEG findings of muscle artifact associated with the movements but no clear EEG correlate. However, given clinical concerns for seizure due to cyanosis and desaturation with the events, patient was given phenobarbital bolus and started on phenobarbital maintenance.
- While on phenobarbital, there was improvement in the events but concern for sedation resulting in increased apneic and desaturation events, so phenobarbital was weaned off and other seizure medications were tried including Levetiracetam, Lacosamide and Fos-phenytoin. The events recurred and were refractory to these medications which prompted re-initiation of phenobarbital.
- As of most recent out patient follow up at 6 weeks of age, phenobarbital dose was increased due to breakthrough events post discharge from NICU.
- Genetic epilepsy panel came back positive for two novel pathogenic variants identified in SLC6A5 gene (refer to Table 1) associated with autosomal recessive hyperekplexia.

TABLES

Table 1. Genetics of hereditary hyperekplexia (HPX)

Gene	Proportion of HPX attributed to gene mutation	Mode of inheritance
GLRA1	61 - 63%	AD or AR
GLRB	12 - 14%	AD or AR
SLC6A5	25%	AR (rarely AD)

GLRA1 (Glycine receptor alpha 1), GLRB (Glycine receptor beta), SLC6A5(Solute carrier family 6 member 5 encoding presynaptic glycine transporter), AD (Autosomal dominant) and AR (Autosomal recessive).

Table 2. Management of hyperekplexia

Type of management	Description
Medications	Clonazepam, Phenobarbital, Phenytoin, Diazepam, and Sodium Valproate.
Therapy	Physical and cognitive therapy can help reduce the fear of falling from sudden startle reflex and thereby improve walking in children.
Vigevano maneuver – Forced flexion of the head and legs towards the trunk in neonates/infants.	Can help stop episodes of hypertonia/tonic spasms.

DISCUSSION

- Hyperekplexia is a rare and underdiagnosed disorder that manifest immediately after birth and improves with age.
- Associated features of hyperekplexia include recurrent neonatal/infantile apnea, developmental delay (delayed motor milestones/speech delay), learning difficulties and epilepsy (estimated prevalence of 7 to 12%).[5]
- Hyperekplexia management includes medications (i.e., Clonazepam, Phenobarbital, Phenytoin, Diazepam and Sodium Valproate), physical and cognitive therapy and Vigevano maneuver – to temporarily stop episodes of hypertonia/tonic spasms in neonates/infants (Table 2).[4,6]

CONCLUSION

- Hyperekplexia with episodes of hypertonia/tonic spasms in neonates can masquerade as neonatal seizures.
- The association of hyperekplexia with sudden neonatal and infant death syndrome underlines the importance for early diagnosis and treatment.

REFERENCES

1. Bakker MJ, van Dijk JG, van den Maagdenberg AM, Tijssen MA. Startle syndromes. Lancet Neurol. 2006;5(6):513-524. doi:10.1016/S1474-4422(06)70470-7
2. Nigro MA, Lim HC. Hyperekplexia and sudden neonatal death. Pediatr Neurol. 1992;8(3):221-225. doi:10.1016/0887-8994(92)90073-8
3. Giacoia GP, Ryan SG. Hyperekplexia associated with apnea and sudden infant death syndrome. Arch Pediatr Adolesc Med. 1994;148(5):540-543. doi:10.1001/archpedi.1994.02170050098025
4. Balint B, Thomas R. Hereditary Hyperekplexia Overview. 2007 Jul 31 [Updated 2019 Dec 19]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1260/
5. Thomas RH, Chung SK, Wood SE, et al. Genotype-phenotype correlations in hyperekplexia: apnoeas, learning difficulties and speech delay. Brain. 2013;136(Pt 10):3085-3095. doi:10.1093/brain/awt207
6. Vigevano F, Di Capua M, Dalla Bernardina B. Startle disease: an avoidable cause of sudden infant death. Lancet. 1989;1(8631):216. doi:10.1016/s0140-6736(89)91226-9

For questions contact
Mahesh Chikkannaiah, MD at
ChikkannaiahM@childrensdayton.org

Scan here to download the e-poster