Hyperekplexia: A Case of Late Onset Startle Syndrome

Amy Fader, DO [1]; Marc Larsen -Hallock, DO [2]; Nicholas Elwert , DO, MS[2]; Cecil Hollen , DO[2]

1: Advocate Christ Medical Center, Oak Lawn, IL/Good Samaritan Medical Center, Rockville Center, NY
2: University of Kentucky, Department of Physical Medicine & Rehabilitation. Lexington, KY

Introduction

Hyperekplexia, an autosomal dominant disorder, is characterized as an excessive startle response to sudden auditory or physical stimuli without habituation. In children, the response manifests as limb jerking predominantly during sleep and in adults, as sudden involuntary muscle contraction followed by a fall. Here we present a case of non-familial, late onset hyperekplexia.

Epidemiology:

Typically rare disorder with genetic origin, both familial or sporadic. It affects 1 in 40,000 in the United States, predominantly affecting women.

Genetics:

Inhibitory glycine receptor subunit A1 (GLRA 1) mutations have been found in both autosomal recessive and dominant individuals. This gene is found on the long arm of chromosome 5 and contributes to the gamma-Aminobutyric acid (GABA) receptor subunit 1 and 2 (GABRA1 And GABRA2). These subunits are used in the production of GABA, glutamate, and nicotinic ACh receptors. These inhibitory glycine receptors are located in the postsynaptic membrane of glycinergic and mixed *y*-aminobutyric acid GABAergic/glycinergic neurons. Other mutations in the GlyT2 (SCL6A5) gene have also been identified, which is responsible for encoding the presynaptic sodium-chloride-dependent glycine transport 2.

Typical patient presentation:

Adults with hyperekplexia typically walk with a wide-based gait and stiff legs without sign of ataxia. The startle response is triggered by auditory, visual, somatosensory, or vestibular stimuli resulting in stiffening of limbs in extensor position, head-retraction, blinking, grimacing, and fall without LOC. They may become wheelchair bound for fear of falling as there is lack habituation with repetitive stimuli. This condition is sometimes associated with psychopathology.

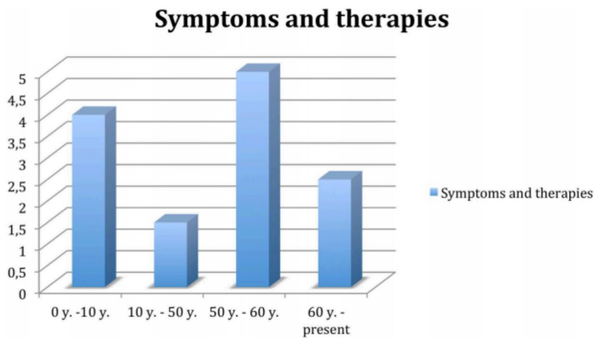

Figure 1: Obtained from Tantonioni A, Peschi G, Granieri E. A Case of Hyperekplexia That Started From Childhood: Clinical Diagnosis With Negative Genetic Investigations. Front Neurol. 2020;11:10. Published 2020 Feb 11. doi:10.3389/fneur.2020.00010

Case

A 76 year old woman with hypothyroidism and anxiety presents with episodic temporary muscle spasticity when startled by loud noises that causes her to fall backward. After falling, she would immediately regain voluntary motor control. This initially started 12 years prior at age 64 without inciting trauma.. She reported this never occurring during her childhood. These startle events progressively became more frequent to occur 2-3 times daily. The fear of falling led her to primarily use a wheelchair for community ambulation. There is no associated loss of consciousness, myoclonus, or postictal periods. Initial treatments with phenytoin and diazepam were unsuccessful. Six years after the first incident, she was prescribed 0.5mg clonazepam twice daily which provided her immediate relief from the startle events. She required one clonazepam dose increase and now only has about two startle events per year.

Family History:

- Mom: Myasthenia gravis, adrenal disease
- Dad: Rheumatoid arthritis
- Neither of her parents, 2 siblings, or 3 kids have this startle response

Previous negative work-up completed:

- 5 polysomnograms
- 72 hour electroencephalogram
- CT/MRI head

Differential Diagnosis:

- Hyperekplexia
- Anxiety/Panic Attacks
- Seizures

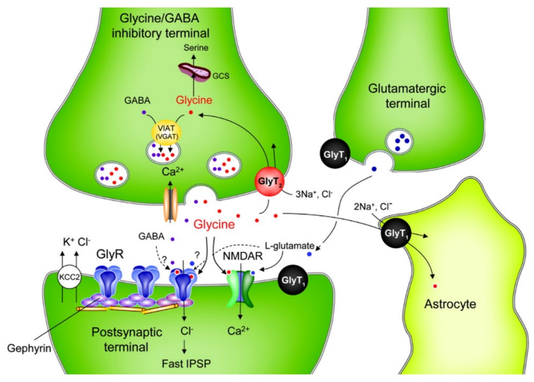

Figure 2: Obtained from Eduardo E. Benarroch: Glycine and its synaptic interactions Functional and clinical implications. Neurology Aug 2011, 77 (7) 677-683; DOI: 10.1212/WNL.0b013e31822a2791

Diagnosis and Treatment

These patients with hyperekplexia demonstrate higher sensitivity, shorter latency, higher muscle response amplitude, and less habituation on electromyography when compared to normal control patients on exposure to acoustic and tactile stimuli. The sternocleidomastoid demonstrates the earliest response after stimuli with an exaggerated response in both the afferent and efferent systems, indicating a brainstem origin to the response. The neurons of the pontine and reticular formation have been documented as being the centers of exaggerated excitability. Unremarkable responses were found in the brainstem auditory and somatosensory pathways. Neuroimaging has little use in the diagnosis of hyperekplexia, but they can exclude structural causes.

Treatment:

The initial treatment for patients with hyperekplexia is a benzodiazepine, particularly clonazepam. For infants/children, recommend weight based dosing at 0.1-0.2 mg/kg/day. For adults, the dosing includes an initial dose of 0.5mg daily and up to 6mg daily. Clonazepam works most often for gene-positive patients (either GLRA1 or GlyT2 positive). It works by enhancing GABA gated Cl^- channel function, thus compensating for the defective channels. It typically works without losing effectiveness over time.

Other medications that may be considered are carbamazepine, phenobarbital, phenytoin, diazepam, 5-hydroxytryptophan, piracetam, and sodium valproate.

Other modalities such as genetic counselling and cognitive behavioral therapy should be considered as hyperekplexia is commonly associated with psycho-pathological disorders.

Discussion

Late onset hyperekplexia is often misdiagnosed, due to its clinical similarity to seizures and rarity affecting 1/40,000 in the United States. Hyperekplexia, typically a genetic mutation in GLRA1or SLC6A5, causes a glycine receptor mutation that prevents the proper cascade of the inhibitory neurotransmitter GABA. By decreasing GABA, there is an overactivation of the basal reticular activating system (RAS), leading to myoclonus with variable stimuli. Thus clonazepam, a benzodiazepine that facilitates GABAergic transmission, provides the necessary inhibition to the RAS and is the standard of treatment. This case is unique as her symptoms presented in adulthood and it was non-familial. With late onset of any startle syndrome, a complete neurological workup should ensue to rule out other neurological conditions. Although genetic testing can be helpful for elucidating the subtype, it does not affect the management.

Conclusion

This patient is a unique case of non-familial hyperekplexia contrasted to a typical inherited neonatal phenotype and demonstrates the need for thorough neurologic work-up and the gold standard treatment, benzodiazepines, for cases of hyperekplexia. Hyperekplexia is often misdiagnosed early on as other diseases such as seizure disorder or anxiety, but this case displays the importance of putting functional myoclonic disorders, like hyperekplexia on the differential.

References

1. Dreissen YE, Tijssen MA. The startle syndromes: physiology and treatment. Epilepsia. 2012 Dec;53 Suppl 7:3-11. doi: 10.1111/j.1528-1167.2012.03709.x. PMID: 23153204.
2. Miyasaki, J.M.. Functional movement disorders.. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2021.
3. Tantonioni A, Peschi G, Granieri E. A Case of Hyperekplexia That Started From Childhood: Clinical Diagnosis With Negative Genetic Investigations. Front Neurol. 2020;11:10. Published 2020 Feb 11. doi:10.3389/fneur.2020.00010
4. Tijssen MA, Voorkamp LM, Padberg GW, van Dijk JG. Startle responses in hereditary hyperekplexia. Arch Neurol. 1997 Apr;54(4):388-93. doi: 10.1001/archneur.1997.00550160034012. PMID: 9109739.
5. Zhou L, Chillag KL, Nigro MA. Hyperekplexia: a treatable neurogenetic disease. Brain Dev. 2002 Oct;24(7):669-74. doi: 10.1016/s0387-7604(02)00095-5. PMID: 12427512.
6. Hamelin, Sophie, et al. "Late onset hyperekplexia." Epileptic disorders 6.3 (2004): 169-172.