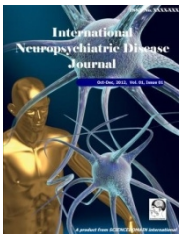

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Novel GLRB Gene Mutation in a Saudi Baby with Hyperekplexia

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Authors' contributions

This work was carried out in collaboration between both authors. Author TMR is the attending doctor who followed the patient all through, tailored management, future plans and wrote the first draft of the manuscript, revised and edited the manuscript. Author AAHM revised the first draft; formulated the initial manuscript and managed the literature searches. Both authors read and approved the final manuscript.

Case Study

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ABSTRACT

Aim: We aim to describe a case of hyperekplexia in a Saudi neonate due to Novel mutation in *GLRB*.
Case Presentation: One month old Saudi neonate with hypertonicity, repetitive episodes of jitteriness and exaggerated startle reflex.
Discussion: Hyperekplexia (OMIM:149400, 138492 & 604159) is considered a rare, autosomal dominant neurological disorder that presents early in life with hypertonicity, exaggerated startle response and life threatening neonatal apnea. It has been caused by mutation in the alpha-1subunit (*GLRA1*) on chromosome 5q32, Beta subunit (*GLRB*) gene on chromosome 4q31 of the inhibitory glycine receptor and *GLYT2* gene (*SLC6A5*) on chromosome 11p15 which encodes a presynaptic glycine transporter.
Conclusion: Raising awareness of the presence of this treatable disease may prevent unnecessary exposure to anti-epileptic medications, prevent life threatening apneas and improve long term outcome.

Keywords: Startle; hyperekplexia; glycine; receptor; stiff baby syndrome.

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1. INTRODUCTION

Hyperekplexia (OMIM:149400, 138492 & 604159) is considered a rare, autosomal dominant neurological disorder that presents early in life with hypertonicity, exaggerated startle response and life threatening neonatal apnea. It has been caused by mutation in the alpha-1 subunit (*GLRA1*) on chromosome 5q32, Beta subunit (*GLRB*) gene on chromosome 4q31 of the inhibitory glycine receptor and *GLYT2* gene (*SLC6A5*) on chromosome 11p15 which encodes a presynaptic glycine transporter.

2. CASE PRESENTATION

He is the first child for first degree cousins, following pregnancy remarkable for vaginal discharges. He was a product of full term pregnancy, the outcome of spontaneous vaginal delivery in a car following a precipitous labor (20 minutes prior to reaching the hospital). He cried immediately. Cord was cut by the emergency team in the car and the baby was found to be active, pink and moving; but cold. He was shifted to the nursery for warming and observation. Birth weight was 3110 grams.

In the nursery, he developed 3 episodes of jitteriness and was admitted to the neonatal intensive care unit (NICU) for further evaluation. After admission, he developed a generalized tonic clonic seizure with cyanosis. This lasted for 15 seconds and was aborted spontaneously. Broad spectrum antibiotics and acyclovir were started. Full septic screen including lumbar puncture (LP) cultures and polymerase chain reaction (PCR) were negative; so antibiotics and acyclovir were stopped.

Electroencephalogram (EEG) was reported as normal; but there were lots of artifacts. Magnetic Resonance Image (MRI) of the brain showed accentuation of T2 hyper intensity of the white matter with loss of normal signal flow void of the mid segment of the superior sagittal sinus. Computed Tomography venography (CTV) showed anomalous drainage of both deep and superficial venous systems. Pediatric neurosurgery consultation advised that no acute intervention is needed at that point in time, and the patient to be followed in the clinic with repeated CTV.

He was started on phenobarbitone (Pb) with fair response, though he started to have convulsions on and off as per his mother. He was discharged on Pb with follow up in pediatric neurology clinic.

At the age of 23 days, he started to have cough, shortness of breath lasting for 4 days. He was admitted to NICU as a case of “Respiratory Syncytial Virus (RSV) - Negative” bronchiolitis, to rule out sepsis. Examination revealed hypertonia more in upper limbs than lower limbs. He was still having abnormal jerky movements which did not respond to loading doses of Pb. When the patient was assessed by the pediatric neurologist, examination revealed one month old baby boy, who looked well, with no dysmorphic features, no neurocutaneous stigmata. He was fixing and momentarily following human faces, moving all limbs symmetrically against gravity. He was startling easily to fine touch with episodes of jitteriness especially on tapping his nose; this could be stopped by neck flexion. His exam was positive for hypertonia (appendicular more than axial). Long term electroencephalogram (EEG) monitoring showed symmetrical, continuous background of theta waves (4-5 Hz) with myogenic artifacts during episodes of sudden flexion of all limbs. During his jitteriness-like episodes, which lasted for 20-30 seconds, artifacts were mainly located in bilateral fronto-

temporal areas. He was diagnosed clinically as a case of neonatal hyperekplexia, started on Clonazepam (Clzp) with good response to titrating dose and he became event free after 5 days. Pb was weaned off over 2 weeks.

Investigations revealed no mutations in *GLRA1* or *SLC6A5* genes. Confirmed mutation in *GLRB* gene was established. Parents did not want to extend further genetic studies (as recommended by the laboratory). Gene dosage analysis by Multiplex ligation-dependent probe amplification (MLPA) {MLPA-Kit P274-A2, MRC-Holland} revealed: No mutation in the *GLRA1 or SLC6A5* genes, No deletion/duplication including/within the *GLRA1 or SLC6A5* genes. Novel mutation c.583C>T, p.Q195*(Substitution – Non sense) in exon 6 of the *GLRB* gene in a homozygous state was confirmed, with no deletion/duplication including/within the *GLRB* gene. PCR amplification and direct sequencing of all coding exons and flanking intronic sequences (*GLRB* gene, Gene Bank NM_000824, 4, NC_000004.11). In our patient the mutation c.583C>T, p.Q195*, in exon 6 of the *GLRB* gene in a homozygous state was detected. No deletion/duplication including/ within the *GLRB* gene.

These results confirm the suspicion of hyperekplexia due to a *GLRB* mutation in our patient. The mutation c.583C>T, p.Q195*, has not been described before to our knowledge (HGMD professional 2012.3). It leads to a pre-terminal stop codon and is expected to result in nonsense-mediated decay of the mutated transcript or in formation of a truncated protein. Therefore, the mutation is very likely to be pathogenic. Since we found no deletion of exon 6 on the second allele, the mutation is clearly present in a homozygous state. The homozygous state in the proband makes autosomal recessive mode of inheritance likely. This could not be confirmed; as the parents were reluctant to do further investigations.

This underscores the susceptibility to having Hyperekplexia with *GLRB* mutation.

To the best of our knowledge and search, this has not been described before. We suggest the association of this mutation with the phenotype but it is still difficult to prove that; due to lack of functional data, lack of ethnicity matched controls.

3. DISCUSSION

An exaggerated startle response may be a component of epilepsy (startle epilepsy) or of a nonepilepti form paroxysmal disorder: namely, hyeprekplexia, or startle disease (also called familial startle disease) [1].

The term hyeprekplexia is derived from Greek, and means exaggerated surprise. Other terms that were used in the past; but not used anymore are: exaggerated startle reaction, hyeprekplexia, stiff baby syndrome, congenital stiff baby syndrome, congenital stiff man syndrome and Kok disease [2]. Kirstein and Silfverskiold first described this entity in 1958 [3]. The clinical manifestations of hyperekplexia consist of: generalized stiffness, excessive startle beginning at birth and a short period of generalized stiffness following the startle reflex. In babies, the muscle stiffening often causes respiratory impairment and apnea that may be fatal [4].

Startle as a response normally exists in normal people. It represents an alerting reaction, with stereotyped features of eye blinking, facial grimacing, flexion of the head, elevation of the shoulders, and flexion of the elbows, trunk, and knees. As an involuntary reflex in infants it appears at the same time as the Moro Reflex [5]. Affected individuals are fully conscious during episodes of stiffness, which consist of forced closure of the eyes and an extension of

the extremities followed by a period of generalized stiffness and sometimes uncontrolled falling [6].

The onset of hyeprekplexia can be manifested from the intrauterine life up to adulthood. Both sexes are equally affected. Hereditary hyeprekplexia has been identified in over 100 pedigrees from Europe, Japan, Canada, the United States, and mostly in northern European descendants [2]. Previously a "major" and a "minor" form of the disease were described, with the minor form being characterized by an excessive startle reflex, but lacking stiffness [6]. There is a genetic evidence for the major form only [6].

Startle responses vary in frequency among individuals and over time. They increase with emotional tension, nervousness, fatigue, and even the expectation of being frightened [6]**.** Exaggerated head-retraction reflex is considered to be a hallmark of hyperekplexia in stiff newborns and adults [7]**.** This is elicited by tapping on the nose. It is found as well in children with cerebral palsy due to severe neonatal asphyxia. Attacks of tonic neonatal cyanosis can be stopped by the Vigevano maneuver, consisting of forced flexion of the head and legs towards the trunk [8]. Not all adults with hyperekplexia have that exaggerated reflex. In daily life, persons with the disease note hypersensitivity in their mantle area.

The differential diagnosis of startle syndromes is extensive; but they lie under three categories: hyperekplexia, stimulus-induced disorders, and neuropsychiatric syndromes [9]. Erroneously, all diseases with a form of exaggerated startling, regardless of their cause, have been named hyperekplexia [10]**.** Some struggle to keep the term hyperekplexia for cases with three manifestations: generalized stiffness at birth, excessive startle reflexes, and generalized stiffness following startle [9]. Additional information from EEG and video registration can help in discriminating different related conditions. In addition genetic studies are of valid benefit; as many stimulus-induced disorders now have an identified gene defect.

Neuropsychiatric syndromes are on the borderland of neurology and psychiatry, and their etiology is poorly understood. These syndromes include startle-induced tics, culture-specific disorders such as Latah, an Indonesian startle syndrome (ticklishness associated with echopraxia and coprolalia) [11]**,** Myriachit (to act foolishly, as reported from Siberia, Asia, and Africa), and jumping Frenchmen of Maine. [12,13].

Genetic studies in hyperekplexia have shown mutations in different parts of the inhibitory glycine receptor (GlyR) with the alpha 1 subunit of the glycine receptor (GLRA1) mutated in about 80% of all pedigrees. The GlyRs are located in the postsynaptic membrane of glycinergic and mixed ϒ-aminobutyric acid (GABA) ergic/glycinergic neurons; they are ligand-gated chloride channels causing postsynaptic hyperpolarization and consequently synaptic inhibition in the brainstem and spinal cord. 20% of cases of Hyperekplexia have missense, nonsense, and frameshift mutations in the *GlyT2* (*SCL6A5*) gene, encoding the presynaptic sodium- and chloride-dependent glycine transporter 2 [14]. Reported are few cases with genetic heterogeneity having mutations affecting other postsynaptic glycinergic proteins, including the beta subunit GlyR (*GLRB*), gephyrin (*GPHN*), and collybistin (*ARHGEF9*) [15]. Most cases of hyperekplexia are an autosomal dominant, with 100% penetrance, and, less often, autosomal recessive trait [16]. Sporadic cases are common and some of these may be congenital [17]. To make a definite diagnosis of hyperekplexia, it is useful to screen for genes that are involved in the glycinergic neurotransmission system [18].

Vigevano maneuver of forced flexion may be lifesaving when prolonged stiffness impedes respiration [19].Treatment modalities include clonazepam (0.1 to 0.2 mg/kg/day) [20,21]. It is mainly used for exaggerated startle than for infantile hypertonicity. Increased tone reverts to normal, and the spontaneous prolonged tonic attacks are almost, but often not completely, abolished. Small doses of clobazam are also effective and well tolerated [22]. Valproic acid has been found to be effective as well; but the risk of hepatotoxicity in neonates and infants is high. A case of neonatal hyperekplexia was reported to respond to levetiracetam after failure of clonazepam [23].

GLRB gene mutations have been previously reported; about 113 mutations are registered within the exome variant server [24]. Most of them are insignificant though a significant proportion due to missense mutation were associated with probably damaging effects [24].

4. CONCLUSION

In our case we report a new gene mutation that enables confirmation of laboratory diagnosis. The latter will be a determining factor of counseling and long term prognosis and treatment. Raising awareness of the presence of this treatable disease will prevent unnecessary exposure to anti-epileptic medications, prevent life threatening apneas and improve long term outcome.

CONSENT

All authors declare that written informed consent was obtained from the patient' parents for publication of this case report.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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