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Novel GLRA1 Variants Causing Neonatal Arthrogryposis and Developmental Delay in Three Unrelated Cases. Early Signs of Autosomal Dominant Hyperekplexia

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ABSTRACT

Hereditary hyperekplexia (HPX) is an inherited neuronal disorder characterized by exaggerated startle responses and stiffness to unexpected stimuli. In the newborn period, the phenotype may present as decreased range of motion of all joints, neonatal arthrogryposis or generalized neonatal hypertonia [1]. HPX is associated with three main genes: GLRA1, GLRB, and SLC6A5 [2]. We report three unrelated families with variants in the GLRA1 gene that expand the understanding of the clinical presentation of affected individuals with GLRA1 variants. No variants observed have been previously reported, two of them are familial and one a de-novo change. One of the families presents three generations of affected individuals with neonatal joint contractures. All three probands in this report present with significant developmental delay, speech delay, feeding difficulties, and motor delay. Hearing loss was seen in one of the patients. All patients appear to present with central hypotonia and two of them present with central hypotonia and peripheral hypertonia with hyperreflexia.

Currently it has been suggested that GLRA1 dysfunction results in failure of inhibition of potent neurotransmitters in the central nervous system [3]. This may explain the intrauterine signs and perinatal presentation of neuromuscular dysfunction in the reported patients. We believe that the information presented here helps to understand the natural history of hyperekplexia. Early recognition of this rare disorder is important due to the high risk of sudden infant death in children due to apnea and the potential to implement rescue treatments. Based on these cases, patients with genetic variants in the GLRA1 gene may present with congenital arthrogryposis that improves with time and results in a milder form of distal joint contractures in adulthood. Patients with hyperekplexia may have a better prognosis than other forms of arthrogryposis and we suggest that GLRA1 gene testing should be included in neonatal arthrogryposis panels.

Keywords

Hyerekplexia, GLRA1, Arthrogryposis.

Introduction

Boris Silfverskiold initially described Hyperekplexia in a Swedish family that presented with "emotionally precipitated drop seizures" [4]. The initial description recognized the exaggerated startle reflex and stiffness at birth seen in affected individuals. In 1993, Shiang and colleagues reported mutations in the glycine receptor subunit alpha-1 (GLRA1) gene as causative of dominant HPX. This was confirmed by Brune and colleagues, who also suggested that null mutations in the GLRA1 gene could cause recessive forms of HPX [5]. Subsequently, the GLRB and SLC6A5 genes have also shown to be associated with clinical findings of HPX [6]. Current perspectives suggest that individuals with GLRB-HPX and SLC6A5 variants are more likely to present

with developmental delay and those with GLRA1 changes may present mild developmental difficulties but severe delay in speech acquisition [2].

Hereditary Hyperekplexia should be differentiated from other genetic neurodevelopmental disorders with an excessive startle response such as early infantile epileptic encephalopathy, Crisponi syndrome, Coffin-Lowry syndrome, GLYT1 encephalopathy, and other disorders of neonatal stiffness [2]. Acquired forms of neonatal stiffness can be seen in post anoxic injury, cerebrovascular events, medullary compression, posterior fossa malformations, and infectious encephalopathy such as clostridium tetani.

We present here three families with heterozygous genetic variants in the GLRA1 gene. One family with a three generation confirmed variant, a second family with a de novo variant and a third family with an intronic maternally inherited variant. All were initially reported as variants of unknown significance; however, it is our impression that the clinical data presented here supports the idea that these variants are pathogenic and are inducing a more severe developmental phenotype than previously described.

Case Report

Case # 1

Patient #1 (Figure 1): The proband was a one-day-old female patient in the neonatal intensive care unit at Peyton Manning Children's Hospital with concerns of multiple congenital joint contractures. She was born at 36 weeks gestation by spontaneous vaginal delivery after a pregnancy complicated by oligohydramnios. Birth weight was 2.72 kg (51st percentile), length 48 cm (68th percentile) and OFC 35.5 cm (98th percentile). Delivery was complicated by a right femoral fracture suspected to occur during extraction. Patient presented with respiratory distress that resolved quickly. Her family history provided by her father was positive for paternal congenital joint contractures that resolved with time. Similar findings were reported for the proband's paternal grandfather. Our physical examination showed a narrow forehead with prominent coronal sutures, mild turricephaly with normal hair distribution, short nose with mild widening of the nasal root, generalized hypertonia with decreased range of motion in all large joints, and shortening of the middle phalanges in all digits with hypoplasia of the fifth toe. The patient has done well overtime, but continues to present mobility limitations. She is being treated with Botox injections by pediatric rehabilitation to improve her joint contractures and she receives orthopedic care due to persistent peripheral spasticity with central hypotonia she is enrolled in early intervention with physical and occupational therapy. A gastrostomy tube was placed for feedings due to oral dysphagia and risk of aspiration. Her developmental assessment with the Kauffman brief intelligence test shows mild cognitive delay with a cognitive score of 77. Head MRI is normal. On her initial evaluation we requested a microarray analysis which was negative and then a whole exome sequencing test which showed a GLRA1 (c.229 G>C; p.G77R) variant that was paternally inherited.

Case # 2

Patient was seen on day one of life by the genetic service at the University of Utah. Family history was not informative. She was the third child born to non-consanguineous parents. She was born by C-section due to non-reassuring fetal heart tones. Pregnancy was complicated by oligohydramnios and breech presentation. Birth weight was 2.305 kg (7th percentile) and length 49 cm (66th percentile) with a head circumference of 34.3 cm (68th percentile). On the initial exam, she had axial hypotonia and contractures of the left wrist and bilateral hips, which were reducible with gentle pressure. Bilateral talipes equino varus was present and the right foot was smaller than the left. Normal creases in hands bilaterally. She was diffusely tremulous and hyperreflexic with sustained clonus. She had a weak suck and a swallow study identified aspiration of thin liquids. An NG-tube was placed due to dysphagia and risk of aspiration. A startle response was not present. Her brain MRI and MR spectroscopy were normal. A nerve conduction study identified decreased amplitudes of the left ulnar and median motor nerves as well as the left deep peroneal motor nerve. EMG and EEG were normal. Creatine kinase was normal. SNP-microarray was normal.

At two months of age, she was admitted to the hospital for failure-to-thrive, irritability and persistent episodes of "hiccupping." She had transitioned to full oral feeds, but weight gain was only 9 grams per day. Her weight and length were at the 0th percentile, while head circumference was at the 24th percentile. On exam, contractures had improved. However, she had developed appendicular spasticity and was diffusely tremulous. She was neither smiling nor tracking objects. Axial hypotonia was persistent. Head control was absent and shoulders were narrow and slumped forward. Scoliosis was present. Currently the patient has shown gain of skills but continues to have global developmental delay with significant dysarthria. A whole exome sequencing trio showed a GLRA1 (c.947C>A; p.Ala316Glu) de novo variant, described as likely pathogenic.

Case # 3

This is a female patient seen initially at the age of 30 months (2.5 years of age) at the Charles E. Schmidt College of Medicine in Florida Atlantic University. She was born at 24 weeks gestation after a pregnancy complicated by preterm labor. Her birth weight was 414gms, length 27 cm and she was considered intrauterine growth restricted. No prenatal findings were reported. Her initial consultation was due to failure-to-thrive, global developmental delay, unilateral hearing loss and short stature. Due to feeding difficulties, the patient required the placement of a gastrostomy tube for weight gain. She has responded to early intervention however, at the age of 43 months she continues to have global developmental delay, verbal apraxia but sound vocalization, facial asymmetry, decreased muscle mass, hypotonia, she does not seat without support, she is unable to stand with support and she does not bear weight on lower extremities. On her initial evaluation a whole exome sequencing showed a maternally inherited intronic variant in GLRA1 (c.913-1G>A) and a gene change in MAGED2 (c.769; p.Arg257Cys (CGT>TGT)).

Table 1: Summary of clinical findings.

Finding	Patient 1	Patient 2	Patient 3
GLRA1 gene variant	c.229 G>C p.G77R	c.913-1 G>A intron 7	c.947C>A p.A316E
Gestational age	36 weeks	37 weeks	24 weeks
Developmental delay	+	+	+
Speech delay	+	+	+
Feeding difficulties	+	+	+
Peripheral hypertonia	+	+	+
Central hypotonia	+	+	+
Joint contractures	+	+	-
Hyperreflexia	+	+	-
Gastrostomy needed	+	-	+
Facial asymmetry	+	-	+
Hearing loss	-	-	+

GLRA1: Glycine receptor subunit alpha-1 gene.

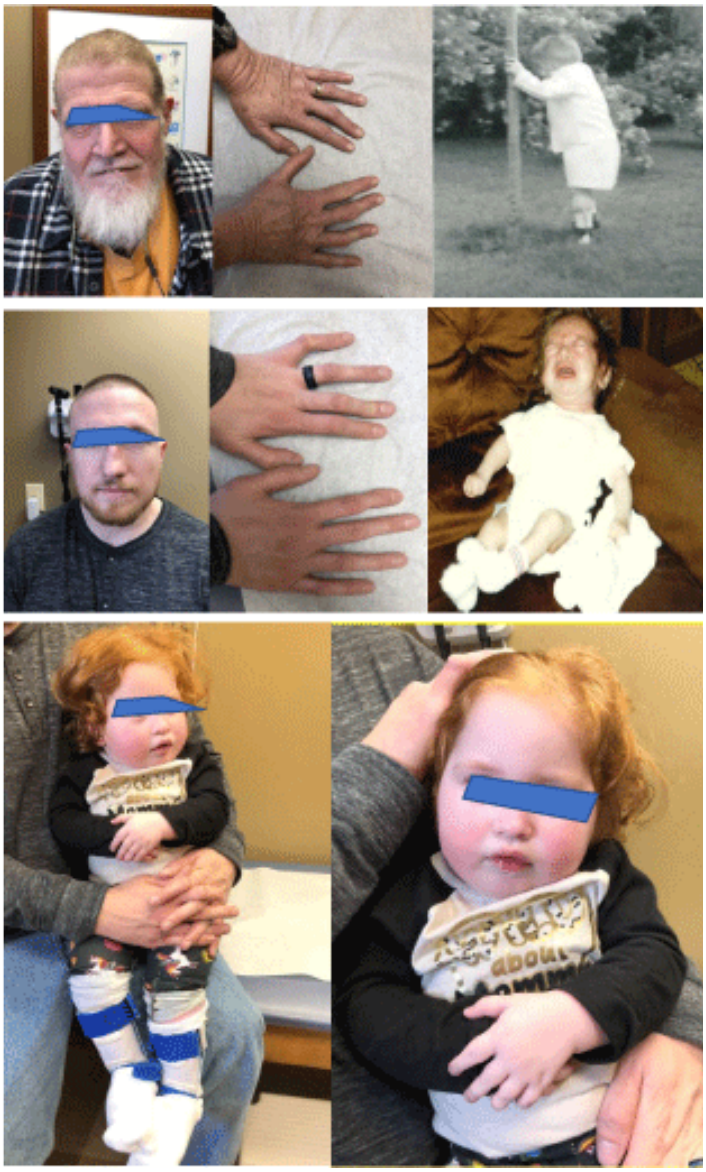
Discussion

The GLRA1 gene encodes the alpha-1 subunit of the glycine receptor, a ligand-gated chloride channel. This inhibitory glycine receptor mediates postsynaptic inhibition in the spinal cord and other regions of the central nervous system [7]. Studies in transgenic mice with point mutations in the alpha-1 subunit of the glycine receptor suggest that variants in GLRA1 may affect gamma aminobutyric acid GABA transmission, which is a major inhibitory neurotransmitter in the central nervous system [3]. Clinically, the lack of inhibition of potent neurotransmitters may result in hypertonia, hyperreflexia and increased startle response. These clinical findings are now recognized as hereditary hyperekplexia.

Approximately sixty to eighty percent (60-80%) of hyperekplexia cases are due to pathogenic variants in the GLRA1 gene. About twenty five percent (25%) are due to changes in the SLC6A5 gene and a smaller number are due to changes in the GLRB, GPHN, and ARHGEF9 genes. Autosomal recessive, dominant and X-linked forms have been documented [2,8,9]. Due to the high variability in clinical presentation and variance in the age of clinical onset, the natural history of HPX is poorly understood. From the clinical point of view, it is reasonable to believe that the lack of neurotransmitter inhibition may lead to abnormal motor development. Motor dysfunction may result in fetal swallowing dysfunction, hypertonia feeding difficulties and joint contractures in the neonate. In addition, life-threatening apnea may occur due to episodes of stiffness leading to risk of sudden infant death.

HPX is rare but also underdiagnosed; it can manifest immediately after birth, and commonly improves with age [10]. Establishing the correct diagnosis early is extremely important so proper management may be initiated to alleviate symptoms and prevent complications in affected individuals. We share here information on three unrelated patient with three different previously unreported variants in the GLRA1 gene who present with severe clinical phenotypes at birth that include severe global developmental delay, joint contractures, significant impaired mobility, feeding difficulties (dysphagia) and in patient #3 unilateral hearing loss. Although all three children are young, their progress has been slow. Our observations suggest that some variants in the GLRA1 gene may represent a severe form of hereditary hyperekplexia.

Figure 1: Case # 1: top row proband's paternal grandfather. Middle row



proband's father, lower row, proband. Notice residual camptodactyly on father and grandfather. Top right: grandfather wearing orthopedic braces. Middle right: father with hand contractions and ankle contractures.

All three reported patients have basic commonalities. However, as they represent different variants we expect to observe some variability. We were able to confirm in patient number one that her father and paternal grandfather had a history of joint abnormalities in childhood that improved with time. However, the photographic evidence suggests that they both have residual findings such as camptodactyly (Figure 1). They both have normal cognitive development and they did not have feeding difficulties early in life. The phenotype in the proband is clearly more severe, and her findings have persisted to her current age of 2.5 years. Case number two has shown positive progress and gain of skills she has recovered oral motor function and she transitioned to full oral

feedings by two months of age. Now at the age of 42 months she is still progressing; she talks in complete sentences, and family provides help occasionally due to mobility issues. She is unable to eat solid food and her calories are mainly provided by her formula diet. Perhaps, the differences in phenotype and progress seen in case 2 may be due to the intronic origin of the variant seen in her case. The other two cases represented exonic variants. From the three cases reported here, patient number three appears to present with the more severe clinical phenotype. At the age of 30 months she presents with severe global developmental delay, she is not able to bear weight, and she is not able to sit by herself. By age 43 months, she continues to present with severe hypotonia and poor muscle mass with vocalization but no words. She had a history of extreme prematurity and an additional genetic variant in the MAGED2 gene, which perhaps both play a role in her clinical outcome.

Our observations raise the question of whether the phenotype seen in our patients should be classified under hereditary hyperekplexia, a severe early onset hyperekplexia, or a provisionally unique syndrome within the GLRA1 spectrum of variants at the molecular level. We suspect that our patients have hyperekplexia, but perhaps the term hereditary hyperekplexia should be revised to neonatal hyperekplexia or early onset hyperekplexia to denote and recognize a more severe form in the newborn period likely associated with GLRA1 anomalies.

Although the entire complexity of the role of GLRA1 in hyperekplexia is not completely understood, the three variants reported here seem to be pathogenic. The variants have not been observed in large population cohorts, have overlapping phenotypes, and were found to segregate with disease in an autosomal dominant pattern with affected individuals, including the three-generation inherited variant identified in-patient #1.

In summary, early findings of hyperekplexia may be confused with other forms of neonatal arthrogryposis. Recognition of the correct diagnosis may have significant implications in the prognosis and early intervention of affected individuals. In severe cases, close monitoring the first year of life is essential due to the risk of lethal apnea. The potential of pharmacologic forms of treatment in the future makes recognition of affected individuals essential to improve their clinical outcomes. Zou et al. [11] suggested that in transgenic mice with glycine receptor abnormalities, rescue treatment with diazepam might be beneficial. In 2020, Zou and his team again suggested that the function of glycine and GABAA receptors are both impaired in hyperekplexia that may be able to be restored by the use of synthetic cannabinoid dehydroxyl cannabidiol. Consideration to include testing for the GLRA1 gene anomalies in the arthrogryposis panels should be given, particularly in the neonatal period.

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