

Familial hyperekplexia: a case report and review of the literature

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Abstract:

Familial Hyperekplexia is a rare but important condition with variable inheritance. It is important to recognize this potentially fatal condition and institute treatment promptly. We are reporting the clinical course and the management of a female neonate born in our unit, with family history of Familial Hyperekplexia.

Key words: Hyperekplexia, Familial Hyperekplexia (FH), Neonatal, Hypertonia, Apnea

CASE REPORT

A baby girl was born to a 31-year-old Para two, gravida one mother at 37 weeks and 5 days of gestation by Spontaneous Vertex Delivery, following induction of labor for decelerations on cardiotocograph. APGAR scores were nine at one and five minutes. Her mother had been diagnosed with hyperekplexia in childhood, carrying a mutation in GLRA 1 gene which was reported “likely to be inherited in an autosomal dominant pattern”. This baby’s birth weight, occipito-frontal circumference and length were 2,400 grams (9th - 25thcentile), 32cm (2nd -9thcentile) and 47cm

(9th centile), respectively. Routine Newborn Examination at 7 hours of age was normal, apart from a history of vomiting after feeds. Subsequent review at 19 hours of age due to the maternal family history of Hyperekplexia revealed “normal cry, global hypertonia, increased neck retraction and increased startle on glabellar and nose taps”. Examination of other systems were normal. The baby was on the hypoglycemic protocol in view of low birth weight and remained normoglycemic. Investigations done in view of hypertonia and increased startle response showed no evidence of sepsis, electrolyte or metabolic abnormalities.

Her mother had a spontaneous abortion at 9 weeks’ gestation in a previous pregnancy. During the current pregnancy, she had experienced periodic per vagina bleeding, a “black out” and urinary tract infections at 13, 19 and 15 weeks respectively. Foetal scans were normal. Maternal routine antenatal serology tests were negative for Hepatitis B surface antigen-HBsAg, Syphilis and HIV. She was a teetotaler, nonsmoker and not a known psychoactive substance user. The baby’s older male sibling and maternal uncle were reported to be carriers of the hyperekplexia gene, but asymptomatic. The baby’s father was

asthmatic while the maternal grandmother had Type 2 Diabetes Mellitus. Both parents were unrelated Caucasians with no history of metabolic disorders.

Baby developed likely physiological jaundice on the second day of life which was treated with phototherapy for two days. Both mother and Baby's blood groups were O-Positive and Baby was direct Coombs test negative. In view of persistent hypertonia, Clonazepam was commenced on the fourth day of life and was discharged home on the thirteenth day of life to be followed up at the Neonatal Clinic.

In early infancy, baby had repeated outpatient visits and admissions to the Hospital. She was seen at 4 and 6 weeks of age for suspected Otitis media and Bronchiolitis. At 7 weeks of age, she was admitted for repeated episodes of "choking, gagging during feeds, vomiting and raspy breathing" consequent to which she was started on Gaviscon® and Ranitidine® for gastro-esophageal reflux with the subsequent addition of Domperidone at 7 months of age. At 9 weeks of age she was readmitted following poor feeding with vomiting, an episode of floppiness, repeated abnormal movements (jerking of extremities, tonic posturing), deviation of gaze to the right and tachycardia. Investigations and monitoring were unremarkable and a retrospective assessment of Hyperekplexic Crisis was made following an initial assessment of seizures. She remained apparently well until 10 months of age when she had varicella which she tolerated without sequelae. Subsequent follow-up showed decreasing hypertonia but transient increase in frequency of startles at 15 months of age following an unrelated accidental fracture of her left ankle. She was discharged and transferred to the Neurological Unit at 21 months of age for follow-up.

Literature Review

Hyperekplexia (HR) is a condition in which there is an exaggerated startle reflex causing apnea, frequent falls and injury.¹⁻³ It can be classified based on severity (minor and major)^{3,4}, and mode of inheritance (familial/hereditary and sporadic).^{3,4} In the minor form of HR startle reflexes are exaggerated from normal while the major type presents with generalized muscular rigidity in the neonatal period.^{3,4}

Familial Hyperekplexia (FH)- Online Mendelian Inheritance in Man (OMIM) 149400 (Synonyms: Familial Startle Disease, Startle Disease, Familial Startle Reaction, Stiffman Syndrome, Congenital Stiffman Syndrome, Congenital Kok Disease and Stiff Baby Syndrome) was first described in 1958.⁵⁻¹⁰ It is a rare, heritable, none epileptic, severe paroxysmal neuromuscular disorder characterized by marked hypertonia and exaggerated responses or startle reflexes to unexpected tactile, auditory and visual stimuli.^{4,7,11,12} Its pathognom is a non-habituating, generalized flexor spasm to a glabellar tap.^{3,8}

In humans, neuromuscular control of reflex actions involves glycine receptors. These strychnine sensitive, nicotinic acetylcholine receptors belong to the superfamily of hetero-pentameric ligand gated ion channels.^{10,13} Human glycine receptors are ligand gated chloride channels that cause post synaptic hyper-polarization and synaptic inhibition in the brain stem and spinal cord.⁸ The disruption of the function of these inhibitory glycinergic receptors increases the general level of excitability of motor neurons, thus accounting for hyperekplexia.⁶ Familial Hyperekplexia is caused by mutations in the genes for pre and post synaptic glycine receptors in the brain, brain stem and spinal cord.^{5,14,15} The

mutations may cause loss of function of glycine receptors, reduced glycine receptor clustering at synapses or reduced glycine release from presynaptic terminals¹⁵. Human glycine receptors are made of 3 alpha- α and 2 beta- β subunits.^{10,13,16,17} Four types of alpha units- α_1 - α_4 and one beta subunit have been identified^{10,13,17}. Mutations of the gene coding for the α_1 subunit in 5q33-35 are more common, accounting for 30% of cases with most mutations found in exons 6 and 7. Mutations of the β subunit have also been described.^{7,8,18,19}

Familial Hyperekplexia may be inherited in an autosomal dominant or autosomal recessive manner.^{3,20} The autosomal dominant type is more common, with almost complete penetrance and variable expressivity.^{3,20,21} Six missense mutations- P250T, Q266H, R271L, R271Q, K276E and Y279L - are inherited in an autosomal dominant manner.⁷ Four-I244N, del Exon 1-6 α_1 subunit gene and compound mutations in the R252H and R392H inherited from both parental alleles are inherited in an autosomal recessive manner.⁷ Other novel mutations resulting in Familial Hyperekplexia have also been described.²²⁻²⁴ Sporadic forms of Hyperekplexia have been described in association with brainstem or extrapyramidal diseases²⁵, paraneoplastic disorders²⁵, encephalitis²⁵, brainstem hemorrhage²⁵, sarcoidosis²⁵, Chiari malformation²⁵ and multiple sclerosis.²⁵ The mechanism/s by which these conditions cause Hyperekplexia are unknown.²⁵ Symptoms of Familial Hyperekplexia usually occur shortly after birth and invariably within the first week of life with generalized hypertonia-attenuating during sleep, myoclonus, trismus and apnea.^{3,4,17,25} Antenatal presentation may occur with abnormal uterine movements or prenatal startle responses.^{3,5,17,25,26} Onset of symptoms in later life have been reported.²⁻⁴ Diagnosis is easily made in a neonate with

Hyperekplexia and a family history of Hyperekplexia. However, this should not preclude a proper diagnostic evaluation, since Familial Hyperekplexia can present in association with other common neonatal causes of jitteriness, apnea and seizures.^{3,9,27,28} Differentials in the neonatal period are hypoglycemia which may co-exist with Familial hyperekplexia⁹, Tetanus^{3,25}, Stiff-Man Syndrome^{1,28}, Myoclonic Seizures³, Disordered GABAergic motor inhibition of motor cortex, brainstem and spinal cord¹, Phenothiazine Toxicity³, Paroxysmal Extreme Pain Disorder⁹ and Crisponi Syndrome.⁹ In adults, differentials include Giles de La Tourette³, Swartz Jampel Syndrome³, Isaacs Mertens³, Reticular Reflex Myoclonus^{3,25} and other obscure pathologies like Jumping Frenchman of Maine³, Miryachit-in Siberia³ and Latah in Malaysia and Indonesia.³

Hypertonia usually resolves spontaneously by the third year of life while excessive startle reflexes persist into adulthood, manifesting as falls unassociated with loss of consciousness.^{4,8,22}

Electroencephalograph and nerve conduction velocities are usually normal,³ while electromyography shows almost permanent muscular activity with periods of quietness.³ No characteristic Computed Tomography findings have been reported.³ Studies using Magnetic Resonance Spectroscopic Imaging have reported normal or reduced relative N-acetyl aspartate(NAA) to Creatinine(Cr) and Choline-Cho ratio (NAA/Cr+Cho) ratio in frontal, central and parietal lobes of affected persons.^{4,29}

Reported associated findings and complications of FH include facial dysmorphism²², central apnea^{3,11}, nocturnal/diurnal/hypnagogic myoclonus^{3,28}, sinus node paucity with bradycardia³⁰, complete heart block³¹, SIDS^{3,11}, umbilical and inguinal hernia^{3,28}, hip dysplasia^{18,28},

pyelectasis^{18,28}, developmental delay^{4,22,28} intellectual disability¹, status epilepticus³², hesitating gait^{1,22}, space phobia^{1,22} and startle induced falls.^{4,5,13,2,33}

Hyperekplexia is a rare illness with varying degrees of severity.³ Familial Hyperekplexia presents in the neonatal period and may lead to death, following apnea, cardiac arrhythmias or cardiac arrest. It has also been implicated in near miss Sudden Infant Death Syndrome and Sudden Infant Death Syndrome,^{30,34-38} with two case series reports documenting 20% mortality.^{37,39} Because of its rarity, large treatment trials are not feasible; hence therapeutic measures are empiric.³⁶ Clonazepam, a benzodiazepine with potent 5-hydroxytryptamine agonist properties, is considered to be the drug of choice for the treatment of hypertonia and apneic episodes in FH.^{3,28,40-42} It considerably reduces or abolishes the occurrence and severity of generalized hypertonia and severe apneas in hyperekplexia with consequent reduction in morbidity and mortality.^{21,27,38} It is presumed to act by potentiating another inhibitory postsynaptic receptor of the Type A GABA.^{3,28,40-42} Other medications that have been used in the treatment of FH with varying results are Carbamazepine, Vigabantrin, Valproic Acid, Alcohol, Phenobarbitone, Chlordiazepoxide, Diazepam, Phenytoin and Piracetam.^{3,28,41} The Vigevano maneuver; forced flexion of the head and legs towards the trunk, can also be employed to abort severe episodes of apnea associated with hypertonia.^{3,40}

Discussion.

Hyperekplexia is a rare disease that may mimic other common neonatal conditions.^{1,3,4,7,9,11,12,25,28} The age and manner of presentation of our neonate was typical^{3,4,17,25} and a diagnosis was easily made, based on maternal history with typical

physical findings on examination, along with negative sepsis and metabolic screens ruling out alternative diagnosis. However, it should be noted that the mother was diagnosed in childhood, implying a delay in maternal diagnosis which is consistent with a case report.^{4,28}

The apparent lack of symptoms in an older male sibling and male maternal uncle carrying the gene is curious, since reports indicated that the proband had a “likely autosomal dominant” inherited type of Familial Hyperekplexia that “usually has complete penetration”. This might be attributed to inheriting an incompletely penetrant gene,³⁶ variable expressivity^{24,28} or modification of expressivity by genes on the Y chromosome. If the sibling has a less expressed form his symptoms may be delayed or remain subclinical.

The response to clonazepam^{3,28,40-42} and subsequent reduction in hypertonia is characteristic and follows the natural course of FH.^{3,4,17,25} The clinical diagnosis of gastro-oesophageal reflux in this patient is unusual, because it is not reported as an association of Familial Hyperekplexia. It also shows the difficulty of distinguishing provoked hyperekplexia from gastro-oesophageal reflux.

Though the baby had an evaluation for Developmental Dysplasia of the Hip-DDH at discharge as part of the normal pre-discharge “baby check”, the authors are of the opinion that babies with HR should also be evaluated for hernia^{3,28}, pyelectasis^{18,28} which are also known associations of FH, in addition to DDH.

The aim of this report is to raise awareness among clinicians of this rare, but potentially mortal disease, with a high likelihood of misdiagnosis, but which, when considered as a differential, can be easily diagnosed and managed. We also recommend that a

differential of hyperekplexia be entertained in babies with unexplained hypertonia.

Parent's consent: Obtained.

Competing interests: None.

Contributors: All authors were involved in preparing the manuscript. All except the first author were involved in management of this child.

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