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Case Report

Congenital myasthenia syndrome due to CHRNA1 mutation resulting in respiratory failure

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ABSTRACT

CMS is an inherited disorder, characterized by defective transmission at Neuromuscular Junction affecting from birth or soon after. It results in fatigue and muscle weakness because of genetic abnormalities that interfere with the neuromuscular junction's ability to function. The most typical signs of CMS include eyelid drooping, breathing difficulties, muscle weakness and weariness with variations depending on specific genetic mutations. Clinical examinations, neurophysiologic tests, and genetic analyses are frequently combined to make the diagnosis of CMS. Although there is no known treatment for CMS, many patients may control their symptoms and lead relatively normal lives with the right care. A newborn with CMS due to CHRNA1 gene mutation is described in this article, along with its very early onset. The CHRNA1 mutation is a rare variant in the Indian population. Due to muscle weakness, the neonate in this case developed severe respiratory distress and later succumbed to death despite rigorous life-saving measures.

Keywords: CMS, Neuromuscular junction, Muscle weakness

INTRODUCTION

Congenital myasthenic syndromes comprise heterogeneous genetic diseases characterized by compromised neuromuscular transmission.[1-3] These are classified as presynaptic, synaptic and post synaptic depending on the location of primary defect within neuromuscular junction. Pre synaptic forms are the rarest, affecting an estimated 7-8% of patients, synaptic forms account for approximately 14-15% and the remaining 75-80% are attributable to post synaptic defects.[4]

Clinical manifestations vary by CMS subtype. Some patients present signs from birth or shortly after whereas others especially those with mild presentations go undiagnosed until adolescence or adulthood. Except for slow channel-congenital myasthenic syndromes, endplate acetyl cholinesterase deficiency and a congenital myasthenic syndrome caused by a defect in acetyl choline resynthesis or packaging , the clinical features of diverse congenital myasthenic syndromes are similar and the precise diagnosis requires the correlation of clinical, invitro electrophysiologic, morphologic and whenever possible molecular genetic studies.[5,6] Neonates commonly presents with respiratory insufficiency with sudden episodic apnea and cyanosis .They can have multiple joint contractures resulting in lack of foetal movements in utero.

Other major findings in the neonatal period may include feeding difficulties, poor suck and cry, choking spells, eyelid ptosis and facial, bulbar and generalized weakness. Stridor in infancy may be an important clue to CMS. In few neonates, they may have long face, narrow jaw, and high arched palate. To date, more than 30 genes have been found to be related to this disease.[7] Approximately 50% of CMS cases were caused by mutations in all subunits of AchR.[8] About 15–20% of cases were caused by a mutation of RAPSN gene, an acetylcholine receptor associated synaptic protein-encoding gene.[9]

CASE REPORT

Here is a case of an early preterm (30 week) baby, born to non-consanguineous couple, G5P1L1A3 mother by lower segment C section with indication being PPROM, Early Hydrops. Antenatal scans showed fetal growth restriction and polyhydramnios. Baby did not cry at birth, had poor spontaneous breathing efforts with APGAR of 4/10 at 1 min, 5/10 at 5 min, hence was intubated in delivery room and shifted to NICU.

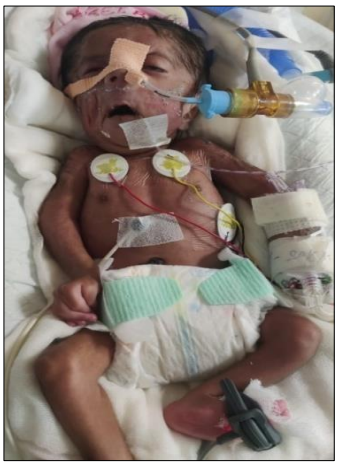

Figure 1: Syndromic facies in CMS.

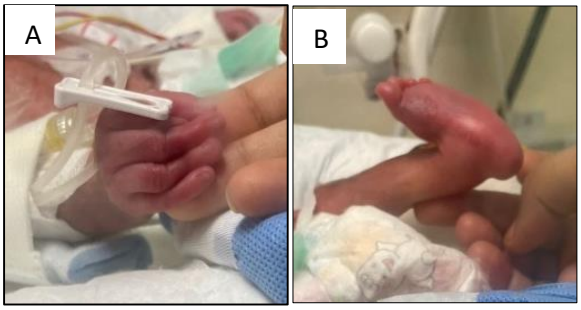

Figure 2: (A, B) Suggestive of arthrogryposis multiplex.

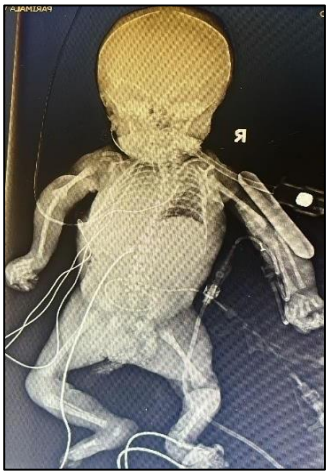

Figure 3: Chest X-ray was suggestive of RDS.

At admission baby was started on IV fluid and partial parenteral admission with amin oven. Baby was started on 2 nd line IV antibiotics (Risk factors–PPROM, Hydrops). On examination, baby had generalized edema, microcephaly, submucosal cleft palate, wide set eyes, micrognathia, hypertrichosis, contractures of multiple joints including elbow, wrist, knee and ankle and hypotonia. Chest X-ray was suggestive of grade 2 RDS (Not requiring surfactant as there was no hypoxemia and oxygen requirement was low on mechanical ventilator) and continued on mechanical ventilation P-SIMV mode. Baby was given extubation trial to CPAP on day 3 of life, but had severe desaturation and bradycardia with poor spontaneous breathing efforts hence was reintubated same day. Further workup was done in view of dysmorphic features. 2D Echo showed no structural abnormalities. Neurosonogram showed bilateral periventricular flare. MRI brain was suggestive of acute to subacute Intraventricular hemorrhage with no malformations. Baby had multiple extubation failures with nasopharyngeal airway and bubble CPAP as baby had no spontaneous respiratory efforts.

Baby was suspected to have myopathy/ neuropathy; hence workup was done for the same. CPK MB was normal (2.6 ng/ml), serum electrolytes were normal (Na-137 mmol/l, K-5.23 mmol/l, Ca-9.24 mg/dl) and planned for Karyotyping and EMG/ENMG. Karyotyping was normal (46, XY). Paediatric neurologist and geneticist opinion was sought for the same, suspected to have arthrogryposis multiplex or Cornelia de Lange syndrome or microdeletion syndrome and was advised to do chromosomal microarray analysis and whole exome sequencing. A homozygous missense variant in exon 5 of the CHRNA1 gene (chr2: g.174754367T>G; Depth: 72x) that results in the amino acid substitution of Proline for Glutamine at codon 131 (p.Gln131Pro;ENST00000348749.9) was detected.

Gene[#] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[$]
CHRNA1 **(-)** (ENST00000348749.9)	Exon 5	c.392A>C **(p.Gln131Pro)**	Homozygous	Fast-channel congenital myasthenic syndrome 1B (OMIM#608930)	Autosomal recessive	Uncertain Significance **(PM2)**

Figure 4: Genetic report of the patient.

DISCUSSION

The acetylcholine receptor (AChR) is a member of the superfamily of transmitter-gated ion channels and plays a critical role in controlling electrical signals between nerves and skeletal muscle cells. In the embryonic development, AChR consists of one β (CHRNB), one δ (CHRND), one γ (CHRNG), and two α (CHRNA1) subunits, but after a gestational age of 33 weeks, the γ subunit is replaced by an ε (CHRNE) subunit (Hesselmans et al). The α subunit of the muscle acetylcholine receptor encoded by CHRNA1 gene is known as the main target of pathogenic autoantibodies in

autoimmune myasthenia gravis. This variant of CHRNA1 which was detected in whole exome sequencing has not been reported in the 1000 genomes, gnomAD (v3.1), gnomAD (v2.1), topmed and in the internal databases. But considering the correlation and consistency with clinical phenotype and it's severity and outcome, we believe that this variant could be pathogenic. Fast-channel congenital myasthenic syndrome (FCCMS) is a disorder of the postsynaptic neuromuscular junction (NMJ) characterized by early-onset progressive muscle weakness. The disorder results from kinetic abnormalities of the acetylcholine receptor (AChR) channel, specifically from abnormally brief opening and activity of the channel, with a rapid decay in endplate current and a failure to reach the threshold for depolarization. However future functional studies are required to clarify the molecular mechanism. Including this variant in future genetic studies and workup as part of genetic counselling may help.

Joshi et al, reported a case of a child who presented with bilateral ptosis, a weak gag reflex, generalized hypotonia with weakness of the intercostal muscles and diaphragm, and depressed deep tendon reflexes, where the child presented with drooping of the eyelids at six months.[8] Another case was reported by Shervin Badav R et al, of a six-month-old patient who presented with episodic respiratory distress and apnea since the 10th day and was diagnosed with congenital myasthenia gravis based on electrodiagnostic findings.[9] Vaidehi Mendpara et al, reported a case of newborn with congenital mysthgenia syndrome (CMG) due to a DOK-7 gene mutation , along with its very early onset. The DOK-7 mutation is a rare variant in the Indian population that causes CMG and usually manifests as 'limb girdle' weakness.[2]

CONCLUSION

Based on the above-mentioned findings, this CHRNA1 variant can be classified as a pathogenically significant variant that maybe included in genetic screenings. Sequencing of this variant in the parents (an invitro strategy) and other affected and non-affected members of the family is recommended to confirm its significance. Such variants maybe detected via further targeted and whole genome sequencing.

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