CASE SERIES

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Congenital myasthenic syndromes: Early to diagnose, early to rise

ABSTRACT

Congenital myasthenic syndromes (CMS) are phenotypically heterogeneous disorders with defects at presynaptic, synaptic, and postsynaptic level. With the worldwide prevalence of CMS unknown, from India either case reports or hospital-based studies give insight into the spectrum of CMS. At present, more than 20 genes have been associated with CMS, majority are CHRNE (50%, including both autosomal dominant and recessive), RAPSN (15–20%), DOK7 (10%-15%), COLQ (10–15%), and GFPT1 (2%). We are reporting four cases of CMS with typical presentation of fatigable ptosis at early age in all patients and limb girdle weakness in two patients. One presented with history of respiratory arrest after fluoroquinolone use. All of them had positive slow rate repetitive nerve stimulation (RNS). Three patients had pathogenic compound heterozygous and homozygous mutations for CHRNE and, one patient had heterozygous mutation for SLC25A1 with uncertain significance. Two patients (one CHRNE and SLC25A1) responded with pyridostigmine only and two patients with homozygous CHRNE mutation responded to pyridostigmine and salbutamol.

Key words: Congenital myasthenic syndrome, CHRNE, Pyridostigmine

INTRODUCTION

Congenital myasthenic syndromes (CMS) had been reported with presentation from severe neonatal forms, arthrogryposis, fatigable ptosis as common presentation and limb girdle weakness in some cases. There were more than 20 genes reported with CMS with defects at presynaptic, synaptic, and postsynaptic regions.[1] The most common defects were seen at acetylcholine receptor, followed by defects at endplate terminal. The phenotypic clues for certain genes as recurrent apneas with CHAR, RAPSN and CHRND pathogenic variants, arthrogryposis multiplex with RAPSN, CHRNA and CHRND pathogenic variants, slow pupillary reflex with COLQ defects, limb girdle weakness with ptosis in DOK7 and isolated limb girdle weakness is associated with pathogenic variants in C-terminal domain in COLQ, late-onset RAPSN variants, and congenital disorders of glycosylation, such as those caused by the genes GFPT1, DPAGT1, ALG2, ALG14, and GMPBB.[1]

There are hospital-based studies from India[2-4] reporting large data on CMS. The Worldwide data on prevalence and incidence of CMS is scarce, with the UK national prevalence of 9.2 per million,[5] there are studies from countries reporting case series or case reports.

As therapies vary from cholinesterase inhibitors (pyridostigmine), potassium channel blockers (3,4-DAP), beta2 receptor adrenergic agonists (salbutamol) to acteylcholine receptor blockers (fluoxetine, quinidine) depending upon the genetic defect. Due to these therapeutic implications, it is necessary to establish the genotype phenotype correlation in each case.[6,7]

We are reporting 4 cases of CMS with fatigable ptosis in all patients, respiratory distress after quinolone use in one patient and limb girls weakness in two patients with CHRNE being common mutation.

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CASE REPORTS

All cases were included from 2019 to 2021 from our tertiary care center. All the patients were evaluated clinically, repetitive nerve stimulation (RNS), and electromyography was done in each case. Acetyl choline receptor antibody was negative in all cases. Targeted gene sequencing done in three cases and mutations identified in these cases. DNA was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to mean >80-100X coverage on Illumina sequencing platform.

Case 1: TW

Seven years old girl presented with history of upper respiratory infection to local GP and received injection ciprofloxacin. She had respiratory arrest for which she has been intubated and ventilated for 24 h. She recovered completely over 24 h. On

recovery she was noticed to have bilateral fatigable ptosis [Figure 1] with mild proximal muscle weakness in both upper and lower limbs. Retrospectively on history, it was revealed that ptosis, external ophthalmoplegia and weakness in limbs were there since 2–3 years. Her slow rate RNS showed positive decrement across orbicularis oculi (OO), trapezius, abductor policis brevis (APB). She was started on pyridostigmine with excellent recovery in ptosis and muscle weakness. On targeted gene sequencing for CMS, a heterozygous single base pair deletion in exon 12 of the CHRNE gene, that results in a frameshift and premature truncation of the protein 64 amino acids downstream to codon 443 was detected (E443ter). The observed variation has previously been reported as a founder mutation in patients affected with CMS in Roma gypsies.[8] There was another novel heterozygous single base pair deletion in exon 12 of the CHRNE gene, that results in a frameshift and premature truncation of the protein 49 amino acids downstream to codon 458 was detected. These CHRNE variations are considered to be compound heterozygous pathogenic variants. The course of illness over the next 3 years was uneventful on pyridostigmine and her parents were informed in detail about avoiding neuromuscular blocking agents in future. Due to persistent limb girdle weakness, she was started on salbutamol in addition to pyridostigmine.

Case 2: SM

Seven years old girl with started with bilateral fatigable ptosis with external ophthalmoparesis since 3 years with no limb girdle weakness. There was no family history. The decrement for slow rate RNS was positive across APB and OO. On electromyography (EMG), no myopathic potentials noted in this case. She was started on pyridostigmine and she is in remission on this for 3 years. On genetic evaluation, a heterozygous missense variation in exon 8 of the SLC25A1 gene that results in the amino acid substitution of Histidine for Tyrosine at codon 256 was detected. A second significant heterozygous variation in the SLC25A1 gene was not detected. This SLC25A1 variation is classified as a variant of uncertain significance and has to be carefully correlated with the clinical symptoms.

Figure 1: Patient TW with bilateral ptosis

Case 3: RD

Twelve years old girl born of a consanguineous marriage, presented with clinical indications of ptosis and limb weakness since 10 years of age. Her sibling is similarly affected. There is positive decrement of postsynaptic neuromuscular defect seen with slow rate RNS across OO and oris in this patient. There is evidence of myopathic potentials noted in the facial muscles in this patient. A homozygous single base pair deletion in exon 7 of the *CHRNE* gene that results in a frameshift and premature truncation of the protein 10 amino acids downstream to codon 204 was detected. This CHRNE variation is classified as a pathogenic variant with autosomal recessive inheritance. This patient responded well to pyridostigmine only and remained independent till last follow-up.

Case 4: AB

Thirty Five years old female presented with bilateral fatigable ptosis and external ophthalmoplegia since 3 years of age. On examination, she has bilateral upper and lower limb proximal weakness, deep tendon reflexes brisk, forearm flexors weak in upper limbs, and external opthalmoplegia with ptosis. She became dependent for her daily activities since 1 year. She was also given steroids and azathioprine considering acquired disorder for brief period before our evaluation. Her slow rate RNS had positive decrement across OO and APB. Additional evidence of myopathic potentials was noted in the proximal and semidistal muscles of upper and lower limbs. She was started on salbutamol with pyridostigmine, became independent after 1 month of treatment. On her genetic evaluation, a homozygous single base pair deletion in exon 12 of the CHRNE gene that results in a frameshift and premature truncation of the protein 64 amino acids down stream to codon 443 was detected same as seen in case 1 [Figure 2].

DISCUSSION

CMS are rare disorders with presentations from neonatal period to adults with common feature being fatigable ptosis and ophthalmoplegia followed by recurrent apneas, limb girdle weakness and slow pupillary reflex in some cases. Genotype phenotype correlation has to be established in each case as there are therapeutic implications in every case. CMS must be differentiated from acquired neuromuscular defects by early onset, negative acetyl choline receptor antibody and in some cases of positive family history.

From India, there are only hospital-based data from centers as Kozhikode (19 cases, no genetics done)[9], Vellore (25 cases), Bangalore (20 cases), and Thiruvanantpuram (21 cases)[2-4] which were showing CHRNE being the most common mutation followed by COLQ, DOK7, MUSK, GFPT1 and RAPSN as other uncommon mutations [Table 1].

Our short case series had similar experience of CHRNE being most common mutation and SLC25A1 as rare mutation

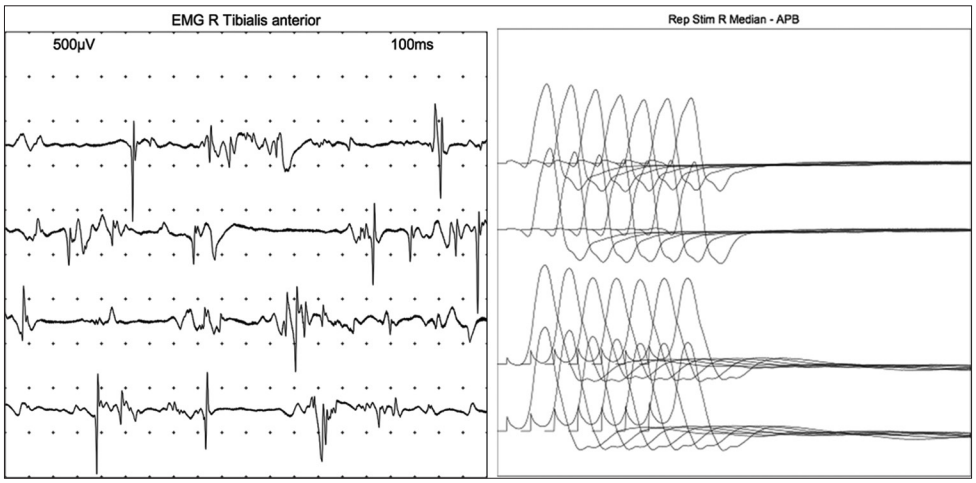

Figure 2: EMG showing myopathic potentials and slow rate RNS showing positive decrement in APB in patient AB

Table 1: Profile of CMS cases

	Clinical features	Genetics	RNS and EMG	Treatment
TW/7 years/F	Ptosis with limb girdle weakness	CHRNE	Positive decrement: APB and OO	Pyridostigmine with salbutamol
SM/7 years/F	Ptosis with external ophthalmoplegia	SLC25A1	Positive decrement: APB and OO	Pyridostigmine
RD/12 years/F	Ptosis with external ophthalmoplegia	CHRNE	Positive decrement: OO with myopathic potentials in facial muscles:	Pyridostigmine
AB/35 years/F	Ptosis with limb girdle weakness	CHRNE	Positive decrement : APB and OO with myopathic potentials in Proximal and semidistal muscles	Pyridostigmine with salbutamol

APB Abductor pollicis brevis, OO: Orbicularis oculi, NA: Not available

Table 2: Comparative data of other Indian studies with present study

	Year	M: F	Mean age of onset	Number	Genetics
Banglore[9]	2018	1:1.1	4.7	20	CHRNE>DOK7>MUSK
Vellore[3]	2018	1.5:1	4.3	25	CHRNE>COLQ>GFPT1>RAPSN
Thiruvanathpuram[4]	2018	1.1:1	4.1	21	COLQ>CHRNE>MUSK
Present study	2021	0:1	3	4	CHRNE>SLC25A1

with female predominance. Acetyl Choline receptor consists of five subunuits as alpha, beta, epsilon and delta. Most of mutations are seen in epsilon subunit with fast channel syndrome. CHRNE codes for the epsilon subunit of the mature, pentameric form of acetylcholine receptor in the postsynaptic membrane of neuromuscular junctions. Pathogenic variants in CHRNE were reported to cause primary acetylcholine receptor deficiency, as well as fast-channel and slow-channel congenital myasthenia. E443ter, a known founder mutation in Roma gypsies,[3] is a null mutation in the cytoplasmic loop preceding the M4 transmembrane region and reduces surface expression of the e subunit. The Romani are a people and culture mostly native to central Europe. There are many sub-groups of Romani people including, Roma, Sinti, Kale, and Manush. Sometimes, Romani people are called Gypsies, although this is not the preferred term. The Romani began to leave India about 1000 years ago. Today, there are an estimated 12–15 million Romani. They live on every continent except Antarctica, some maintaining nomadic lifestyles and some in settled communities. The largest concentration of Romani is in southeastern Europe and Russia.[8] The founder mutation (c.1327delC) in this case again proves the theory of Roma migration. Accordingly, in two cases (TW and AB) who harbor E443ter (c.1327delC), the symptoms are consistent with acetylcholine receptor deficiency, and responded significantly to pyridostigmine like other patients with acetylcholine receptor deficiency. But in these cases due to significant limb girdle weakness, addition of salbutamol helped significantly

in improving the weakness. This mutation has been reported earlier in three cases from CMC vellore study.

All of the patients has good prognosis with significant recovery with pyridostigmine with doses from 30 mg twice daily started initially an dose required reached upto 60 mg thrice daily and in two cases salbutamol helped in improving the limb girdle weakness. Early diagnosis in these cases helped to better prognosticate and treatment with appropriate drugs. As pyridostigmine helps in CHRNE, fast channel syndrome, RAPSN mutations and it worsens clinical condition in patients with DOK7, COLQ and slow channel syndrome, genetics to be considered as first investigation in suspected cases. Salbutamol in dose of 4 mg once daily helped in two cases significantly with limb girdle weakness suggesting role in CHRNE mutations to be considered early [Table 2].[10]

As treatment was given for 2–3 months only, long-term response is still awaited.

CONCLUSION

CMS being one of the rare neuromuscular disorders when diagnosed in early stage has good prognosis. Genetics with targeted gene sequencing with focus on relevant genes could lower the cost of these tests in future. Electrophysiology must include not only RNS also EMG in each case as patient 4 (AB) has myopathic potentials in semidistal and distal muscles, which might suggest role of salbutamol to be used early in such cases. Childhood onset, generalised limb girdle weakness, bony deformities, decremental response on slow rate RNS, and absence of AchR antibodies should be considered under CMS and salbutamol can be added as secondary adjuvant in selected cases (till genetic diagnosis is reached). Hence, it can save patients from unnecessary immunosuppresants and thymectomy. Pyridostigmine for ptosis and salbutamol for limb girdle weakness in CHRNE as well as in COLQ and DOK7 leads to significant recovery.

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