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Congenital Myasthenic Syndrome: case study from a tertiary care institute of Western India

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ABSTRACT

Objective. To describe clinical characteristics, genetic details and management of patients of congenital myasthenic syndrome.

Methods. A retrospective study was carried out from 2020 to 2023. Patient who presented with ptosis, ophthalmoplegia, proximal limb weakness with genetically confirmed mutations for CMS were included in the study. Patients who were positive for Acetylcholine receptor antibody (AChRAb) or Muscle specific kinase (MuSK) antibody or any other antibodies suggestive of acquired myasthenia were excluded from the study.

Outcome. 6 genetically proven patients were identified out of which 4 patients had CHRNE mutation, 1 patient had CHRNA1 mutation and 1 patient had Dok7 mutation. Mean delay in diagnosis was 15 years. Patient with Dok 7 mutation responded to salbutamol, 1 patient of CHRNE mutation required combination of pyridostigmine, fluoxetine and salbutamol, rest all patient responded to pyridostigmine. It took 4 weeks for improvement after starting salbutamol in patient with Dok7 mutation.

Conclusion. Although rare, CMS is potentially treatable group of disease. Patient presenting with early onset muscular weakness should be evaluated thoroughly and CMS should be considered in presence of eyelid ptosis, ophthalmoplegia and proximal weakness with diurnal fluctuations. RNS and genetic testing are paramount in achieving an early diagnosis.

Keywords: myasthenia, acetylcholine receptor antibody, congenital myasthenic syndrome, muscle specific kinase

List of abbreviations

AChRab	– Acetylcholine receptor antibody	MuSK	– Muscle specific kinase
CMS	– Congenital myasthenic syndrome	NCS	– Nerve Conduction Study
EMG	– Electromyography	RNS	– Repetitive Nerve Stimulation
LGMD	– Limb-girdle muscular dystrophy		

INTRODUCTION

Congenital myasthenic syndromes (CMS) are rare inherited disorders affecting the neuromuscular transmission [1]. Symptom onset is usually at birth or early childhood [1]. Patients develop fatigable ocular, bulbar or limb–girdle weakness; and often have positive family history [1]. Depending on location of primary defect within neuromuscular junction, CMS can be classified as Presynaptic, synaptic or postsynaptic [2]. Germline pathogenic variants in about 35 genes have been reported (ALG14, AGRN, ALG2, CHRNA1, CHRNB1, CHRND, CHRNE, CHRNG, CHAT, COL13A1, COLQ, CHD8, DPAGT1, DOK7, GMPPB, GFPT1, LAMA5, LAMB2, LRP4, MYO9A, MUSK, PLEC, PURA , PREPL, RPH3A, RAPSN, SNAP25, SCN4A, SYT2, SLC18A3, SLC25A1, SLC5A7, TOR1AIP1, UNC13A, and VAMP1) [3]. Management and prognosis differ for each subtype of CMS and therefore its important identify CMS subtypes based on clinical features, electrophysiology and genetic analysis [4].

On review of literature, there are few studies of CMS from India. We have presented our experience with small cohort of CMS in this article.

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METHODS

We carried out a retrospective study in a single tertiary care institute of western India. Duration of study was from 2020 to 2023.

We have included patient who presented with ptosis, ophthalmoplegia, proximal limb weakness with genetically confirmed mutations for CMS.

Patients who were positive for Acetylcholine receptor antibody (AChRAb) or Muscle specific kinase (MuSK) antibody or any other antibodies suggestive of acquired myasthenia were excluded from the study. Informed consent was obtained from subjects or their legal guardian.

RESULTS

Total 6 patients fulfilled the inclusion criteria and clinical details, treatment given and genetic analysis has been summarized in the Table 1.

Case 3 – 49 years old male presented with bilateral fatigable ptosis, restricted extra-ocular movements and fatigable limb weakness. He was worked up for myasthenia gravis. He had decremental response on 2-3 Hz RNS. Acetylcholine receptor antibody and Musk Antibody were negative. He was started on immunosuppressants to which he did not respond. He also underwent thymectomy. His siblings, elder sister (case 4) and his younger brother (case 5) had similar complaints but they did not consult any neurologist due to mild symptoms. Genetic analysis confirmed CHRNE mutation in all 3 siblings. Limb weakness of all 3 siblings responded to pyridostigmine. However, there was partial improvement in ocular symptoms.

TABLE 1. Clinical characteristics and genetic details of all patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	M	M	M	F	M	F
Age at onset	Birth	Birth	29 years	30 years	26 years	Birth
Age at diagnosis	14 years	13 years	49 years	56 years	36 years	8 years
Ptosis	Y	Y	Y	Y	Y	Y
Ophthalmoplegia	N	Y	Y	Y	Y	Y
Proximal limb weakness	Y	Y	Y	Y	Y	Y
Treatment	Salbutamol	Pyridostigmine Salbutamol Fluoxetine	Pyridostigmine	Pyridostigmine	Pyridostigmine	Pyridostigmine
Gene	DOK7	CHRNE	CHRNE	CHRNE	CHRNE	CHRNA1
Location	Exon 7	Exon 12	Exon 12	Exon 12	Exon 12	Exon 9
Variant	c.1124_1127dup (p.Ala378SerfsTer30)	c.1327delG (p.Glu443LysfsTer64)	c.1327delG (p.Glu443LysfsTer64)	c.1327delG (p.Glu443LysfsTer64)	c.1327delG (p.Glu443LysfsTer64)	c.1259C>T (p.Ala420Val)

Abbreviations: N-No , Y-Yes , M-Male , F-female

Case 1 – 14 years old male child presented with limb girdle pattern of weakness for 4 years of age. He had ptosis since birth which was non fluctuating. Patient was diagnosed to have LGMD. Parents came to our center in view of significant progression and for any advanced treatment if available. CMS was considered in view of asymmetric ptosis which is an uncommon finding in LGMD. His RNS was normal, ice pack test was negative, clinical exome was sent which showed DOK7 mutation. Patient was treated with salbutamol. On one month follow up, he showed dramatic improvement in his symptoms.

Case 2 – 13 years old male, presented with weak cry at birth. Parents noticed ptosis at 6 months of age and fatigable limb weakness at 2 years of age. He was worked up for myasthenia gravis. Acetylcholine receptor antibody, Musk antibody was negative. RNS was normal. Genetic analysis revealed CHRNE mutation. Initially he responded to pyridostigmine but after 3-4 years additionally required salbutamol and fluoxetine.

Case 4 – 8 years old female, presented with weak cry at birth, delayed motor milestone. Parents noticed bilateral ptosis, ophthalmoplegia and proximal limb weakness at 4 years of age. She underwent work up for myasthenia gravis. Acetyl choline receptor antibody and Musk antibody were negative. RNS was normal. Genetic analysis revealed CHRNA1 mutation. Limb weakness responded to pyridostigmine with partial response of ocular manifestation.

DISCUSSION

Clinical analysis

The Age of onset of disease in our study was from birth to 30 years. Mean time from onset of symptoms to diagnosis in our study was 15 years. This might be due lack of clinical suspicion owing to rarity of dis-

ease, unwillingness and non affordability for genetic testing.

Mean delay in diagnosis reported from other studies is 6 years in Khadilkar et al [5], 23 years in study by Wargon and colleagues [6], 12.5 ± 9.9 years in study of large cohort of CMS from southern India [7].

One patient (case 4) was being treated as Myasthenia Gravis and was on immunosuppressant agent for long duration and even underwent thymectomy. Immunosuppressant could be stopped for him after the correct diagnosis of CMS was made.

One patient (case 1) was diagnosed clinically as Limb Girdle Muscular Dystrophy due to non fluctuating pure motor limb girdle pattern of weakness. In contrast to Myasthenia gravis, diurnal fluctuations of muscle strength and muscle fatigue are not always observed in CMS [3]. However asymmetric left eye ptosis was diagnostic clue in favor of CMS.

Diurnal fluctuations of external ophthalmoplegia are associated with diplopia in Myasthenia Gravis, but not always CMS. This may be possibly due to presence of external ophthalmoplegia since infancy, which enables compensation for the fluctuating visual axes [3]. In our study case 2 and case 6 did not complain of diplopia despite having external ophthalmoplegia.

Investigations

In our study all patients had normal NCS/EMG study. In completely resting muscle and in absence of medication effect (due to cholinesterase inhibitors), demonstration of repetitive CMAP is specific for diagnosis of CMS [8]. Repetitive CMAP is seen End-plate AChE deficiency (synaptic defect) and slow channel syndrome (post synaptic defect) [8].

Repetitive nerve stimulation at 2-3 Hz showed decremental response in case 3,4,5 and 6.

Anti-AchR and Anti-MuSK antibodies are negative in patients with CMS [9]. In our study, case 2,3 and 6 were tested negative for Anti acetylcholine receptor antibody and anti Musk antibody. These antibodies were not tested in case 1,4 and 5.

Genetic analysis

In our study most common mutation found was CHRNE which correlates with findings of study of large cohort of CMS done in southern India where most common affected gene was CHRNE followed by DOK7, DPAGT1, GFPT1, MUSK, GMPPB, and COLQ [7].

Mutations in CHRNE and CHRNA1 can cause Primary AChR deficiency, fast channel syndrome or slow channel syndrome [4]. Patients with primary AChR deficiency predominantly have ptosis, ophthalmoparesis and moderate to severe limb weakness [4,9]. Slow channel syndrome has severe involvement of forearm, scapular and cervical muscles with relative sparing of ocular muscle [4,9]. Weakness of wrist and finger extensor and neck muscle points towards slow channel syndrome [4,9].

Acetylcholinesterase inhibitors are useful in AChR deficiency and fast channel syndrome. Other drugs which can be used in AChR deficiency are salbutamol, amifampridine [4]. Fluoxetine is useful in slow channel syndrome [4].

In our study all patients with CHRNE mutation and CHRNA1 mutation had proximal fatigable limb weakness, bilateral fatigable ptosis and external ophthalmoplegia. Case 3,4,5, and 6 had improvement in limb weakness with pyridostigmine with partial improvement in ocular symptoms. Case 2 additionally required salbutamol and fluoxetine

Dok 7 is a muscle protein that activates MuSK which leads to Rapsyn-associated endplate AChR clustering and normal folding of postsynaptic membrane [10]. Onset of symptoms ranges from childhood to adulthood. It presents mainly with limb girdle pattern of weakness, waddling gait and ptosis but no ophthalmoplegia which correlated with clinical features of our patient (case 1) [9]. AChE inhibitors can worsen symptoms and should be avoided in Dok-7, slow Channel and COLQ gene mutation [4]. Salbutamol (0.1-0.3 mg/kg/d in children up to 6 years and 6-18 mg/d in adults) is effective for patients of Dok7 CMS [11]. In our patient it took 4 weeks for improvement after starting salbutamol, which correlates which finding found in study done by Khadilkar et al where improvement was seen on an average of 3-5 weeks [5].

CONCLUSION

Although rare, congenital myasthenic syndrome is potentially treatable group of disease. Patient presenting with early onset muscular weakness should be evaluated thoroughly and CMS should be considered in presence of eyelid ptosis, ophthalmoplegia and proximal weakness with diurnal fluctuations. RNS and genetic testing are paramount in achieving an early diagnosis and initiating treatment to prevent further muscle injury and disability. Larger multi-centric Indian studies are needed for comprehensive information on the subject.

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