Congenital myasthenic syndromes: Natural history and long-term prognosis

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Abstract

Introduction: Congenital myastenia syndrome (CMS) is a rare, heterogeneous group of genetically determined, disorder of neuromuscular transmission. They have a varied presentation and progression and very few studies have addressed the natural history. Aim of the present study is to describe the clinical profile and natural history of patients with CMS. Materials and Methods: Study includes patients with CMS who attended comprehensive-neuromuscular-clinic (CNMC) during the period January, 2000-2008 with a minimum follow-up of 2 years, with inclusion criteria: (1) Onset in infancy or childhood with fluctuating ocular, bulbar, respiratory or limb muscle weakness (2) Acetylcholine receptor antibody negative (3) normal computed tomography (CT) thymus (4) Abnormal repetitive nerve stimulation (RNS) testing (5) Exclusion of other autoimmune disorders. Results: Out of 314 patients with myasthenia who attended the CNMC during study period, 15 (4.8%) were with CMS (8 boys, 7 girls). Patients were divided as infantile and childhood onset. The mean age of onset and diagnosis in infantile and childhood onset groups were 5.5 months/3.1 years and 3.6 years/6.5 years respectively. Eleven patients had ptosis and 4 had generalized presentation. Most common site of decremental response was over facial nerve in 12 (75%) patients. All patients showed good response to treatment with acetyl cholinesterase inhibitor with stable course on follow-up without exacerbations. Mean dose for neostigmine was 28 mg/day and for pyridostigmine was 153 mg/day. Conclusion: Ptosis is most common symptom at onset in CMS, emphasizing importance of RNS of the facial nerve, in the absence of molecular diagnosis of CMS. Our CMS cohort had relatively stable course without intermittent exacerbations with fair response to acetyl cholinesterase inhibitor.

Key Words

Acetylcholine receptor deficiency, congenital myasthenia syndrome, ocular myasthenia

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Materials and Methods

Study included patients with CMS who attended comprehensive-neuromuscular-clinic (CNMC) during the period 2000-2008 with a minimum follow-up of 2 years, with following inclusion criteria; (1) Onset in infancy, childhood with fluctuating ocular, bulbar, respiratory or limb muscle weakness (2) Acetylcholine receptor (AChR) antibody negative (3) normal CT thymus (4) Repetitive nerve stimulation (RNS) study and/or (5) neostigmine test performed. Patients with other autoimmune disorders were excluded. A detailed neurological examination including fatigability test for ocular and limb muscles was done. A detailed family history and whenever possible examination of family members was done. The patients underwent the following tests: Thyroid function tests, serum creatinine phosphokinase, levels, total and differential leukocyte count, erythrocyte sedimentation rate, X-ray chest, computerized tomography of chest and AChR antibody estimation. Anti-Musk antibody which is also essential for exclusion of autoimmune myasthenia, although Musk–positive myasthenia gravis (MG) is very rare in children was not performed due to non-availability as well as economic constraints.

Repetitive nerve stimulation

The electrophysiological tests done were after determining supramaximal stimulation intensity and measurement of amplitude of compound muscle action potential (CMAP) of orbicularis oculi, abductor pollicis brevis and trapezius. We also looked for repetitive CMAP, which is characteristically seen in some forms of CMS. After obtaining a baseline CMAP with supramaximal stimulation, the muscle being studied is exercised with maximal voluntary contraction against resistance for 10 s. Immediately after the 10 s exercise, a single supramaximal stimulus is given and the amplitude of the CMAP is compared to the baseline study. This technique increases presynaptic calcium concentration resulting in facilitation of ACh release. RNS of these muscles at 3 Hz stimulation as per protocol which involves pre- and post- exercise RNS testing at 3 Hz and whenever required high-frequency stimulation as tolerated by the patient was done. If required detailed nerve conduction study and electromyography were also done on individual basis.

Results

Out of 314 patients with myasthenia who attended the CNMC during study period, 15 (4.8%) were with CMS, 8 boys and 7 girls. Patients were divided into infantile-onset (less than 1 year) and childhood-onset (more than 1 year up to 12 years) In infantile group, mean age of onset was 0.55 years and mean age at diagnosis was 3.1 years, while in childhood-onset group mean age of onset was 3.6 years and mean age at diagnosis was 6.5 years (range 1-6 years) [Table 1]. Mean delay in diagnosis from onset of symptoms in infantile group was 2.6 years and 2.9 years in childhood onset. Eleven patients had ocular and four had generalized presentation. Most common ocular symptom was ptosis and normal extra-ocular movements were present in seven patients (46.6%). Four patients (26.6%) had total ophthalmoplegia.

| Table 1: Clinical characteristics of patients with congenital myasthenia syndrome |
|---------------------------------|-----------------|-----------------|-----------------|-------|
|                                  | Infantile onset | Childhood onset |
|                                  | n=4 (%)         | n=11 (%)        | Total n=15 (%)  | P value |
| Age of onset (years)             | 0.55            | 3.1             | 3.6             |       |
| Age at diagnosis (years)         | 2.6             | 6.5             | 6.5             |       |
| Delay in diagnosis               | 2.9             | 11              | 73.3            | NS    |
| Ocular                           | 2               | 9               | 81.8            |      |
| Combined                         | 2               | 2               | 18.2            | 26.7  |
| Delayed mile stones              | 4               | 10              | 18.2            | 40    | 0.011 |
| Positive neostigmine test        | 2               | 2               | 71.4            | 7     | 87.5  |
| Facial nerve RNS                 | 3               | 6               | 9               | 12    | 75    | NS    |
| Spinal accessory nerve RNS       | 2               | 50              | 2               | 18.2  | 26.7  | NS    |
| Ulnar nerve RNS                  | 2               | 33.3            | 1               | 9.9   | 3     | 20    | NS    |
| Crisis                           | 0               | 0               | 1               | 9.9   | 1     | 66.7  | NS    |
| Deformity                        | 1               | 25              | 1               | 9.9   | 2     | 13.3  | NS    |
| Total ophthalmoplegia            | 1               | 25              | 3               | 27.2  | 4     | 26.7  | NS    |
| Normal extra ocular movements    | 3               | 75              | 4               | 36.4  | 7     | 46.7  | NS    |

RNS=Repetitive nerve stimulation, NS=Not significant

Family history of CMS was present in one patient. Developmental milestones were delayed in six patients (40%) with motor delay as the predominant symptom. All patients with infantile onset had delayed milestones. One patient had psychomotor retardation due to prematurity and birth asphyxia. Facial dysmorphism was present in one patient and scoliosis was present in two patients. No patient had any wasting or contracture. All patients had normal tone except one, who had hypotonia. Deep tendon reflexes were normal in all patients. Out of nine patients in whom neostigmine test was performed, seven patients showed positive results. Most common decremental response was seen in the facial nerve (12 patients), followed by spinal accessory nerve (four patients) and ulnar nerve (three patients). None of the patient had repetitive CMAP to single nerve stimulation. Thirteen patients were started on treatment with acetyl cholinesterase inhibitor with fair response and stable course on follow-up without exacerbations. Two patients did not require any treatment as symptoms were non-disabling. Eight patients received only pyridostigmine, four received neostigmine and one patient received both. Mean neostigmine dose was 28 mg/day and pyridostigmine dose was 153 mg/day. Mean duration of follow-up was 4.6 years (range 2-12 years). Only one patient developed myasthenic crisis following severe infection on follow-up at the age of 25 years which was managed with supportive treatment and intravenous immunoglobulin (IVIg) due to sepsis. There are no guidelines for treatment of myasthenic crisis in CMS patient, which are rare and usually managed with supportive treatment. The improvement in our patient could have been spontaneous or due to IVIg. His repeat AChR antibody was negative. One patient had a complex partial seizure and one had ostium secondum atrial septal defect, which was corrected.
Discussion

CMS has been classified as pre-synaptic, synaptic and post-synaptic depending upon genetic defects in molecules expressed at the neuromuscular junction. Some of the mutations identified are (1) choline acetyltransferase (ChAT) that resynthesizes acetylcholine from recycled choline at the nerve terminal, (2) collagen Q (COLQ) that anchors acetylcholine esterase to the synaptic basal lamina, (3) AChR subunits α, β, δ, ε (AChR deficiency, slow channel syndrome, fast channel syndrome), (4) muscle-specific kinase (MuSK) that transmits the AChR-clustering signal from agrin/LRP4 to rapsyn/AChR, (5) Dok-7 that transmits the AChR-clustering signal from agrin/ LRP4/MuSK to rapsyn/AChR, (6) rapsyn that anchors and clusters AChRs at the neuromuscular junction (7) agrin that is released from the nerve terminal and induces AChR clustering by stimulating the downstream LRP4/MuSK/Dok-7/rapsyn/AChR pathway. Most of the CMS have autosomal recessive inheritance except slow channel variety, which is dominant and genetic mutations can be identified in only about 60% of the CMS patients. The age of onset, pattern of weakness, the treatment response and the disease course over time depends upon the molecular mechanisms arising from mutations. ChAT is presynaptic, COLQ is synaptic while rest are post-synaptic genes.\[8\]-\[11\]

Patients with mutations of fast channel, ChAT, AChR subunits (predominantly epsilon) and COLQ present at birth or early in infancy. Ophthalmoplegia is commonly reported in fast channel, ChAT, AChR sub-units mutations. Contractures are seen in slow channel and rapsyn has mild arthrogryposis multiplex congenita, dysmorphism and/or the presence of a high arched palate. Mutations of the AChR subunits, rapsyn are relatively stable over time, although all the CMS may worsen temporarily with infections. Most of the mutations of the AChR sub-units (predominantly epsilon) derive from an ancient founder mutation in the Indian subcontinent. A double CMAP response to single nerve stimulation is noted in the majority of COLQ CMS but is also reported in the slow channel syndromes.\[11\]

Results from this study highlight some important aspects of CMS. All cases except one were sporadic while in most of the studies sporadic cases are rare and familial cases are common. Although dysmorphic features have been commonly described in Iranian and Iraqi Jews, only one of our patient had dysmorphic features.\[10\] Our patient had an elongated face, low set ears and high-arched palate [Figure 1a and b]. Facial malformations may be secondary to the neuromuscular defect or may be primary and unrelated. The mean age of onset was 2.7 years (range birth-15 years), which correlates with CMS though few may have late presentation as late as second decade as in one of our patients who had onset of symptoms at the age of 15 years.\[11\] Mean delay in diagnosis was 2.6 years in infantile onset and 2.9 years in childhood form. Many a times, the CMS is misdiagnosed as congenital myopathy, central hypotonia or neurometabolic diseases, myasthenia gravis, limb–girdle or congenital muscular dystrophy and spinal muscular atrophy.\[15\] Delayed milestones were seen in 40% patients with predominant motor delay in our series while 54% patients had delayed milestones in a study by Kinali et al.\[13\] In our study, all patients in infantile onset group had delayed milestones, indicating that a CMS patient should be monitored for developmental delay.

Patients presenting in neonatal age group may present with hypotonia and apnea and may be misdiagnosed as anoxic seizures and may suffer from recurrent apnea with subsequent hypoxic brain damage leading to delayed development. CMS should be suspected in the neonates who present with feeding difficulties, hypotonia with or without limb weakness, ptosis, respiratory insufficiency, contractures and stridor.\[14\] Electrophysiology showed most common decremental response in facial nerve (75% patients) suggestive of most common ocular involvement. This emphasizes the need for evaluating decremental response in facial nerve in patients with CMS before documenting that the RNS is negative. Thirteen patients were started on treatment with acetyl cholinesterase inhibitor with fair response and stable course on follow-up. Only one patient developed crisis similar to the study by Schara et al.\[15\]

Treatment in CMS depends on underlying defect in neuromuscular transmission. Most patients with Fast-channel or Endplate AChR deficiency respond favorably but incompletely to cholinesterase inhibitors. Most patients treated with 3,4-di- amino pyridine (DAP) combined with pyridostigmine have favourable response.\[16\] Patients with Rapsyn Deficiency and Dok-7 respond well to pyridostigmine\[17\] with some additional benefit from the use of 3,4-DAP\[18\] or ephedrine. The slow-channel syndromes are usually treated with quinidine and fluoxetine, which are long-lived, open-channel blockers of AChR that shorten the duration of channel opening in a concentration dependent manner.\[19\], \[20\] Clinical profile of our patients is suggestive of post-synaptic defect and is likely to be due to mutations of the AChR subunits, rapsyn and fast channel although molecular analysis is not available. The limitation of our study is lack of genetic studies and testing for anti-Musk antibody, although Musk–positive MG is very rare in children.

CMS are usually associated with a favorable prognosis if it occurs beyond neonatal period with early diagnosis and appropriate treatment. It is clear that our series from a specialized tertiary referral center may represent the CMS patients with post-synaptic defect due to selection biases and these observations particularly apply to our cohort.

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**Figure 1: Patient with elongated face, low set ears and high-arched palate**
Conclusion

Ptosis is most common symptom at onset in CMS. So we emphasize in the absence of molecular diagnosis the importance of performing RNS of the facial nerve. Our CMS cohort had a relatively stable course without intermittent exacerbations and with fair response to acetyl cholinesterase inhibitor.

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