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Original Article

Different Aspects of Congenital Myasthenic Syndromes in Childhood

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ABSTRACT

Objective: Congenital myasthenic syndrome (CMS) is a heterogeneous group of diseases that are not immune-mediated. It is caused by structural defects in different synaptic proteins of neuromuscular transmission as a result of different mutations. CMS is classified according to the location of the mutant protein as presynaptic, synaptic basal lamina-associated, or postsynaptic. In this study, we aimed to help further the knowledge of this issue by analyzing the clinical features and treatment responses of patients with an extremely rare condition of CMS.

Methods: The clinical information of 13 patients who attended the CMS clinic at Mersin City Training and Research Hospital and Aydın Maternity and Child Hospital were reviewed. After considering the clinical diagnosis in all our cases, we performed a genetic diagnosis with whole exon sequencing or a CMS panel.

Results: Of the 13 patients included in this study, 11 (84.6%) were males and 2 (15.4%) were females. The mean age of our patients was 73.30±60.56 months, and the mean age at the time of diagnosis was 44±49.15 months. In our patients diagnosed with CMS, 9 (69.2%) COLQ mutations, 2 (15.4%) CHAT mutations, 1 (7.7%) RAPSN mutation, and 1 (7.7%) SCN4A mutation were observed. Ephedrine was started in 8 of the 9 patients with COLQ mutations, and a good response was obtained. A good response to treatment was not observed in those patients who were started on pyridostigmine.

Conclusion: CMS can often be confused with other neuromuscular diseases. In patients presenting with ptosis, bulbar findings, apnea, and muscle weakness, CMS should be prediagnosed, and a genetic examination should be performed on these patients.

INTRODUCTION

Congenital myasthenic syndrome (CMS) is a heterogeneous group of diseases defined in the group of childhood neuromuscular diseases.[1] CMS, like other myasthenic diseases, is not of immune origin. It is caused by structural defects in different synaptic proteins of neuromuscular transmission as a result of different mutations.[2–4] In Western countries, the annual incidence is found to be 30/1 000 000. It has been calculated as 1–5 per million under the age of 20 years, and the symptoms of 44.8% of cases have started at or before the age of 14 years.[5,6] In recent years, whole exome sequencing (WES) has helped with the diagnosis of novel CMS cases. WES has accelerated in pace, and so far, many genes related to CMS have been identified. Based on the location of the mutant protein, CMS is classified into three subtypes: presynaptic, synaptic basal lamina-associated, and postsynaptic.[7]

In this study, we present the clinical and molecular genetic findings of 13 patients diagnosed with CMS. The considerable size of the group studied enables us to further define the phenotypic and genotypic spectrum of CMS.

MATERIALS AND METHODS

The clinical information of 13 patients who attended the CMS clinic at Mersin City Training and Research Hospital and Aydın Maternity and Child Hospital were reviewed. The patients had convincing evidence of CMS on the basis of their clinical features, neurophysiological studies, and laboratory investigations (including measurement of AChR antibodies and serum creatine kinase). After considering the clinical diagnosis in all our cases, we made a genetic diagnosis with whole exon sequencing or CMS panel. In this study, we compiled the clinical findings of those patients diagnosed with CMS according to the mutation type. Venous blood samples were drawn from the patients and their unaffected relatives for DNA extraction. Genomic DNA was isolated using a blood DNA extraction kit according to the manufacturer's recommendations (Promega, Mannheim, Germany).

Before collecting the data, written consent was obtained from the patients, and approval was given by the local ethics committee and the institution where the study was conducted.

Statistical analysis

The data obtained from the study were evaluated using the SPSS 22.0 program. In the analysis of descriptive statistics, numbers and percentages are given for categorical variables, and mean, standard deviation, minimum, maximum, and median are given for numerical variables.

RESULTS

Of the 13 patients included in the study, 11 (84.6%) were males and 2 (15.4%) were females. The mean age of our patients was 73.30±60.56 months, and the mean age at the time of diagnosis was 44±49.15 months. In our patients diagnosed with CMS, 9 (69.2%) COLQ mutations, 2 (15.4%) CHAT mutations, 1 (7.7%) RAPSN mutation, and 1 (7.7%) SCN4A mutation were observed. Electromyography was able to be performed on 8 of the patients. No response was obtained in 1 of these 8 patients, and the decremental response was obtained in 7 of these patients. Anti-MuSK and acetylcholinesterase tests were carried out in 10 of the patients, and all were found to be negative (Table 1).

All of our patients had ptosis, and 7 (53.8%) had bulbar findings. Twelve (92.3%) of our patients had weaknesses, and 1 (7.7%) was on a continuous mechanical ventilator with a tracheostomy. The respiratory function between episodes was normal in the other patients except for the patient who was connected to a mechanical ventilator. Ten of our patients (76.9%) had frequent recurrent lower respiratory tract infections. Apnea episodes were present in both the patients with the CHAT mutation, the one patient with the RAPSN mutation, and 1 of the 9 patients with COLQ mutations. Both patients with the CHAT mutation and the patient with RAPSN mutation had arthrogryposis, and one of the patients with the COLQ mutation had fecal and urinary incontinence. The mental and cognitive functions of 5 (38.5%) of our patients were normal. Four patients had mild and 4 had moderate mental and cognitive retardation. Ephedrine was started in 8 of the 9 patients with COLQ mutation, and a good response was obtained. Salbutamol was started in the remaining patient because ephedrine could not be found and partial response was obtained. A significant reduction in weakness was observed in those patients receiving ephedrine treatment. Those patients who were started on pyridostigmine did not exhibit a good response (Table 2).

DISCUSSION

CMS is a genetic, heterogeneous neuromuscular disease with some abnormalities in the synaptic transmission system. To date, all stages of neuromuscular transmission (presynaptic, synaptic, and postsynaptic) genetic defects have resulted in syndromes with different clinical and sometimes simple, often electrophysiological features. Increasingly in recent years, a gene panel for WES is being used in the diagnosis of CMS.[7,8] In our study, most of the patients were diagnosed by means of WES.

Numerous COLQ mutations have been described. As a result of the COLQ mutation, acetylcholinesterase deficiency in the end-plate synaptic membrane and a corresponding increase in acetylcholine in the synaptic area are observed.[9,10] In our study, the COLQ mutation was the most common mutation. Very different clinical findings were observed in the patients. In one comprehensive study of patients with various COLQ mutations, neonatal manifestations were evident in the majority, including ptosis, ophthalmoparesis, hypotonia, poor cry and suck, and some respiratory problems.[11] Generalized hypotonia is seen in COLQ mutations, but more noticeable in proximal and truncal muscles, as highlighted by Müller et al.[12] In this study, patients with COLQ mutations had ptosis, varying

Table 1. Gender, age, genetic, and electrophysiological findings of patients

Patient	Gender	Age at diagnosis (months)	Current age (months)	Causative gene	Location	EMG	Anti-MuSK	Acetylcholinesterase
1	M	5	24	COLQ	Synaptic	None	None	None
2	M	30	42	COLQ	Synaptic	Decremental response	Negative	Negative
3	M	19	37	COLQ	Synaptic	Decremental response	Negative	Negative
4	F	33	40	COLQ	Synaptic	Decremental response	Negative	Negative
5	M	24	36	COLQ	Synaptic	None	Negative	Negative
6	M	144	204	COLQ	Synaptic	No response	Negative	Negative
7	M	60	78	COLQ	Synaptic	None	None	None
8	M	10	22	COLQ	Synaptic	Decremental response	Negative	Negative
9	M	30	60	COLQ	Synaptic	Decremental response	Negative	Negative
10	F	19	39	CHAT	Presynaptic	None	Negative	Negative
11	M	12	38	CHAT	Presynaptic	None	None	None
12	M	6	76	RAPSN	Postsynaptic	Decremental response	Negative	Negative
13	M	120	156	SCN4A	Synaptic	Decremental response	Negative	Negative

M: Male; F: Female; EMG: Electromyography; Anti-MuSK: Anti-muscle-specific tyrosine kinase.

Table 2. Clinical findings and treatment responses of patients

Patient	Mutation	Cranial muscles	Weakness	Additional features	Cognition	Recurrent LRTI/apnea	Respiratory function between episodes	Ephedrine/salbutamol response	Pyridostigmine response
1	COLQ	Ptosis, bulbar	Yes	None	Normal	Yes/yes	Normal	Ephedrine/Good response	Worseness
2	COLQ	Ptosis	Yes	None	Moderate	Yes/no	Normal	Ephedrine/Good response	Worseness
3	COLQ	Ptosis, bulbar	Yes	None	Moderate	Yes/no	Normal	Ephedrine/Good response	No response
4	COLQ	Ptosis, bulbar	Yes	None	Normal	Yes/no	Normal	Ephedrine/Good response	Worseness
5	COLQ	Ptosis	Yes	None	Normal	Yes/no	Normal	Ephedrine/Good response	Worseness
6	COLQ	Ptosis	Yes	Incontinence	Normal	No/no	Normal	Ephedrine/Good response	No response
7	COLQ	Ptosis, bulbar	Yes	None	Normal	No/no	Normal	Ephedrine/Good response	Worseness
8	COLQ	Ptosis, bulbar	Yes	None	Mildly impaired	Yes/no	Normal	Ephedrine/Good response	Worseness
9	COLQ	Ptosis, bulbar	No	None	Moderate	No/no	Normal	Salbutamol/Mildly response	No response
10	CHAT	Ptosis, bulbar	Yes	Arthrogryposis	Mildly impaired	Yes/yes	Normal	No ephedrine/salbutamol	No response
11	CHAT	Ptosis, bulbar	Yes	Arthrogryposis	Mildly Impaired	Yes/yes	MV support	Salbutamol/No response	No response
12	RAPSN	Ptosis	Yes	Arthrogryposis	Mildly impaired	Yes/yes	Normal	Salbutamol/No response	No response
13	SCN4A	Ptosis, bulbar	Yes	None	Moderate	No/no	Normal	No ephedrine/salbutamol	No response

MV: Mechanic ventilation.

degrees of weakness, and bulbar findings. The synaptic effects caused by the COLQ mutation are somewhat improved by some B2-sympathomimetics such as ephedrine. Ephedrine improves walking distance and ventilatory function in some patients, including those with DOK7 and COLQ mutations.[10] In our study, a good response was obtained with ephedrine treatment in those patients with COLQ mutations. Only one patient received a mild response after salbutamol treatment because his family could not provide ephedrine.

Choline acetyltransferase (CHAT) mutation causes presynaptic CM. Presynaptic CMS types usually present with dyspnea, apnea, arthrogryposis, ventilator dependence, fatigue, ptosis, and bulbar paralysis.[13] In our study, our patients with CHAT mutation had a severe weakness, ptosis, bulbar findings, and arthrogryposis. One of our patients was connected to a mechanical ventilator. CMS that develops as a result of CHAT mutation responds seriously to pyridostigmine treatment. Pyridostigmine treatment provides respiratory support, which can help improve clinical symptoms and prognosis.[14] In our study, we did not get a response from pyridostigmine in those patients with CHAT mutations.

Unlike the CHAT mutation, RAPSN is responsible for the postsynaptic CMS.[15] Two different phenotypes associated with RAPSN have been described. RAPSN is responsible for arthrogryposis, hypotonia, apnea, and feeding difficulties in the early infantile period. The other is the late-onset type presenting during childhood, or even in adulthood, with generalized weakness and sometimes wasting of upper limb muscles.[16] The complaints of our patient with RAPSN mutation started in the infantile period. Our patient had ptosis, bulbar findings, apnea, and arthrogryposis. Our patient did not respond to pyridostigmine and salbutamol. Congenital myopathy and myotonia, alternating hemiplegia, periodic paralysis, and CMS diseases are seen due to mutations in various regions of the SCN4A gene. Loss-of-function mutations of SCN4A are present in CMS.[17] This type of CMS presents with bulbar weakness, ptosis, and respiratory difficulties. Our patient also had ptosis and bulbar findings, but did not have a history of apnea.

CONCLUSION

In conclusion, CMS is a group of disorders caused by mutations in genes that encode proteins responsible for the function and integrity of the neuromuscular junction. CMS can often be confused with other neuromuscular diseases. In patients presenting with ptosis, bulbar findings, apnea, and muscle weakness, CMS should be prediagnosed and genetic examination should be performed on these patients.

Ethics Committee Approval

This study was approved by the Mersin Provincial Health Directorate Clinical Research Ethics Committee (Date: 24.06.2021, Decision No: 2021/6-17).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: MA.; Design: S.K., M.A.; Supervision: S.K.; Fundings: M.A.; Data: M.A., S.K.; Analysis: M.A.; Literature search: S.K.; Writing: M.A.; Critical revision: S.K., M.A.

Conflict of Interest

None declared.

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Çocukluk Çağındaki Konjenital Miyastenik Sendromların Farklı Yüzleri

Amaç: Konjenital Miyastenik Sendromlar (KMS), farklı mutasyonlar sonucu nöromüsküler iletinin sinaptik proteinlerindeki farklı yapısal bozukluklara neden olduğu, immün aracılı olmayan heterojen hastalıklar grubudur. KMS, mutant proteinin konumuna göre presinaptik, sinaptik bazal lamina ile ilişkili olan ve postsinaptik olarak sınıflandırıldı.Bu çalışmada son derece nadir bir durum olan KMS tanılı hastaların klinik özelliklerini ve tedavi yanıtlarını değerlendirerek daha ileri çalışmalara yardımcı olmayı amaçladık.

Gereç ve Yöntem: Mersin Şehir Hastanesi ile Aydın Kadın Doğum ve Çocuk Hastanesi'nde halen KMS kliniğine başvuran 13 hastanın klinik bilgileri gözden geçirildi. Tüm olgularımızda klinik tanıyı değerlendirdikten sonra tüm ekzon dizilimi veya KMS paneli ile genetik tanı koyduk.

Bulgular: Çalışmaya alınan 13 hastanın 11'i (%84.6) erkek, 2'si (%15.3) kız çocuklardı. Hastalarımızın tanı anında yaş ortalaması 73.30±60.56 ay, yaş ortalaması 44±49.15 ay idi. KMS tanısı alan hastalarımızda 9 (%69.2) COLQ, 2 (%15.4) CHAT, bir (%7.7) RAPSN ve bir (%7.7) SCN4A mutasyonu gözlendi. COLQ mutasyonu olan 9 hastanın 8'ine efedrin başlandı ve iyi yanıt alındı. Tüm hastalarda pridostigmin başlananlarda tedaviye iyi yanıt alınamadı.

Sonuç: KMS sıklıkla diğer nöromüsküler hastalıklarla kolayca karışabilir. Pitozis, bulber bulgular, apne ve kas güçsüzlüğü ile başvuran hastalarda KMS ön tanısı akla gelmeli ve bu hastalarda genetik inceleme düşünülmelidir.

Anahtar Sözcükler: CHAT; COLQ; Konjenital Miyastenik Sendromlar; RAPSN; SCN4A.