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CASE REPORT

Case report of congenital myasthenic syndrome due to CHRNE mutation diagnosed in adulthood*

Fatma Bilgili[1], **Fatma Nur Elyıldırım**[2], **Serpil Yıldız**[2]

[1]Department of Neurology, Ardahan Public Hospital, Ardahan, Türkiye
[2]Department of Neurology, Bolu Abant İzzet Baysal University, Bolu, Türkiye

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ABSTRACT

Congenital myasthenic syndromes are a rare subgroup of neuromuscular diseases caused by genetic defects in proteins involved in the structure, function and repair of the neuromuscular junction. Although these syndromes usually start in the neonatal and childhood periods, they may rarely start in adulthood. Because the clinical and laboratory findings of congenital myasthenic syndrome that starts in adulthood closely resemble those of seronegative myasthenia gravis, a differential diagnosis between the two is essential. This differential diagnosis is clinically important because treatment approaches and drug responses differ between the two diseases. Here, we aimed to draw attention to this disease and increase clinical awareness by presenting a case of congenital myasthenic syndrome diagnosed in adulthood.

Keywords: CHRNE, congenital nyasthenic syndrome, neuromuscular diseases

INTRODUCTION

Myasthenia, first described by Friedrich Jolly in 1895, is a clinical syndrome characterized by diffuse muscle weakness that can be acquired or inherited and affects transmission at the neuromuscular junction (1). Myasthenia gravis (MG) is a classic example of an antibody-mediated autoimmune disease that occurs frequently in adults. Autoantibodies targeting acetylcholine receptors (AChR), muscle-specific kinase (MuSK), low-density lipoprotein receptor-related protein 4 (Lrp4) and agrin have been identified in its pathogenesis (2). If no antibodies are detected, it is defined as seronegative myasthenia gravis (2). Congenital myasthenic syndrome (CMS) is a form of myasthenia that usually occurs in newborns and early childhood due to various genetic mutations (3). Clinical symptoms in CMS can be heterogeneous, depending on the underlying genetic mutation and the affected site at the neuromuscular junction (presynaptic, synaptic or postsynaptic) (4). Although

Corresponding author: Fatma Bilgili **E-mail:** fatmabilgili19@gmail.com
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rare, CMS can initially present in adulthood and closely mimic seronegative myasthenia gravis, both clinically and on electromyographic (EMG) evaluation (3). It is important to distinguish between CMS and myasthenia gravis due to differences in treatment and drug responses. We present a case of congenital myasthenic syndrome diagnosed in adulthood to highlight this underrecognized condition and raise awareness among clinicians.

CASE REPORT

A 22-year-old male patient presented with fatigue for the last 3 years and ptosis of the right eyelid in the evening for the last 5-6 months. On detailed history-taking for myasthenic syndromes, the patient reported no additional complaints. The patient had visited an ophthalmologist once during childhood because of difficulty fully opening his eyes, but no diagnosis was established at that time. There were no other remarkable features in the patient's medical history. There was no family history of similar disorders; however, the patient's parents were first cousins. Neurologic examination was normal. Detailed blood tests were normal and acetylcholine receptor antibodies were negative. Other antibodies associated with myasthenia gravis could not be analyzed because they were not available for testing at our institution. Cranial and cervical magnetic resonance imaging (MRI) showed no pathologic findings. EMG examination showed a more than 10% decremental response in the nasalis muscle with repetitive nerve stimulation at a frequency of 3-5 Hz. We requested genetic testing for congenital myasthenic syndromes because of a history of suspected childhood ptosis. Genetic analysis revealed a pathogenic homozygous mutation in the CHRNE gene.

DISCUSSION

CMS is a rare, clinically and genetically heterogeneous disorder of juvenile and adult onset caused by abnormalities in the structure and function of the neuromuscular junction (1). Data on the prevalence of CMS are limited and are derived primarily from isolated case reports. To date, only a limited number of CMS patients have been identified in Turkey, and the genotypic and phenotypic characteristics of CMS in this population remain unclear (5). According to a recent study, the prevalence of CMS is estimated to be 1/10 of that of myasthenia gravis, corresponding to 25-125 per million (4). The prevalence of CMS has been reported to vary between ethnic groups and regions. This variation may be due to the mild nature of CMS symptoms and diagnostic delays caused by its differential diagnosis with many other conditions (4,6,7). CMS is a rare disorder, with even rarer forms in which symptoms begin in adulthood, as observed in the patient presented above. Differentiating these patients from those with seronegative MG is challenging but critical, given the decisive implications for treatment. Weakness, particularly affecting the eye, bulbar, and proximal extremity muscles; symptoms extending from birth to early childhood; a positive family history; a negative antibody test profile; clinical and neurophysiological myasthenic findings; EMG findings consistent with neuromuscular junction dysfunction; and an inadequate response to immunotherapy and acetylcholinesterase inhibitors all suggest a diagnosis of CMS (3). Myopathy is another important diagnosis to consider, particularly in patients with late-onset limb-girdle muscle weakness who lack the more typical findings of CMS, such as ptosis and marked restriction of eye movement. However, even when elevated serum creatine kinase (CK) levels and myopathic changes on EMG are present, these patients should still be evaluated for CMS (5).

CMS is clinically characterized by abnormal fatigue or temporary or permanent weakness of extraocular, facial, bulbar, trunk, respiratory or limb muscles. Onset may be intrauterine or congenital, or may occur in infancy or childhood, and rarely in adolescence or adulthood. Severity ranges from mild muscle weakness to respiratory failure and early death (4). Although all CMS subtypes share common clinical features such as fatigue and muscle weakness, the age of onset, specific symptoms, and treatment efficacy may differ depending on the underlying genetic defect and associated molecular mechanisms (8). Treatment options and evaluations based on genetic subtype are given in Table 1 (8).

The structures affected within the neuromuscular junction due to genetic mutation are shown in

Table 1. Congenital myasthenic syndromes: A clinical and treatment approach

Syndrome	Treatment	Notes
AChR deficiency (*CHRNE*)	3,4-DAP, pyridostigmine	Albuterol is an important add on agent
AChR kinetic defect: fast channel syndrome	Pyridostigmine, 3,4-DAP	Avoid quinidine and fluoxetine; beta-adrenergic agonists may be an important adjunct
ALG2 and ALG14 myasthenia	Pyridostigmine	3,4-DAP might confer added benefit
ChAT deficiency	Pyridostigmine; parenteral neostigmine for apneic episodes	Even asymptomatic patients should be treated due to risk of fatal apnea. Severe phenotype may not respond to cholinergic drugs and may require permanent ventilatory support and apnea monitor; beta-adrenergic agonists may be an important adjunct
DPAGT1 myasthenia	Pyridostigmine	May respond to add on 3,4-DAP and albuterol
GFPT1 myasthenia	Pyridostigmine, 3,4-DAP	May see additional improvement with an add on adrenergic agents such as albuterol or ephedrine
GMPPB myasthenia	Pyridostigmine	May see additional improvement with added 3,4-DAP, albuterol
MUNC13-1 myasthenia	3,4-DAP	Perhaps improvement with add on pyridostigmine
MYO9A deficiency	Pyridostigmine	Respiratory crises have occurred following intake of 3,4-DAP and fluoxetine
PREPL deficiency	May respond to pyridostigmine early in life	
Rapsyn deficiency	Pyridostigmine, 3,4-DAP	Albuterol may be helpful as an add on treatment; worsening with fluoxetine reported
SCN4A sodium channel myasthenia	Pyridostigmine	Acetazolamide also can mitigate periodic paralysis due to mutations in the same gene
SLC5A7 deficiency	Pyridostigmine	Treats episodic apnea
SNAP25 deficiency	3,4-DAP	Improves weakness, not ataxia Not pyridostigmine
Synaptobrevin-1 myasthenia	Pyridostigmine may be helpful	
Synaptotagmin-2 myasthenia	3,4-DAP	Pyridostigmine ineffective in a small study
VAChT or (*SLC18A3*) myasthenia	Pyridostigmine	Moderate improvement
AChE deficiency (COLQ)	Albuterol or ephedrine	Avoid pyridostigmine and 3,4-DAP
Agrin deficiency	Ephedrine	No response to cholinergic agents
DOK7 deficiency	Albuterol or ephedrine	Avoid pyridostigmine
LRP4 deficiency	Albuterol	Avoid cholinergic agents
MuSK defect	Albuterol Variable response to 3,4-DAP	Pyridostigmine conventional doses may worsen symptoms
AChR kinetic defect: slow-channel syndrome	Fluoxetine, quinidine	Avoid cholinergic agents

*This table is adapted from the study ' Congenital Myasthenic Syndromes: a Clinical and Treatment Approach' by Farmakidis C. et al.

Table 2 (1). Of the 32 genes identified to date to be associated with CMS, mutations in six of them (CHRNE, RAPSN, COLQ, DOK7, GFPT1, and CHAT) account for approximately 90% of cases (3,4). The CHRNE gene encodes the epsilon subunit of the acetylcholine receptor (AChR) and its mutation leads to a deficiency of acetylcholine receptors or abnormal channel kinetics. To date, the most frequently reported mutation in CMS has been in this gene (9). The most common mutations in Turkey are those that cause AChR deficiency (particularly the c.1219+2T>G mutation in the CHRNE gene) (5).

Most patients with CHRNE mutations present with mild, progressive bulbar, respiratory or diffuse limb weakness, often accompanied by ptosis or ophthalmoplegia at birth. However, the type and severity of clinical manifestations can vary considerably between affected families (4,10). Repetitive nerve stimulation (RNS) may show a decremental response or appear normal, while single fiber EMG (SF-EMG) may show increased jitter (4,11). Most patients respond well to acetylcholinesterase inhibitors (AChEIs), but in some, pyridostigmine and 3,4-Diaminopyridine (3,4-DAP) may be ineffective or may worsen their condition. In some cases, albuterol or salbutamol alone can be highly effective. Fluoxetine alone may be ineffective, but its combination with salbutamol may give better results (4,9,11).

Early diagnosis of this condition, which cannot be reliably distinguished from myasthenia gravis due to overlapping clinical features and findings, is crucial to ensure appropriate treatment. In suspected cases, a definitive diagnosis can only be established through genetic testing. In our case, the childhood onset of symptoms and the suspicious clinical presentation led us to request genetic testing. The genetic test results identified the most common CHRNE mutation, consistent with data from Turkey. After receiving the genetic test results, we started our patient on fluoxetine treatment and observed an improvement in his symptoms.

Through this case, we aimed to contribute to the limited body of literature on congenital myasthenic

Table 2. Classification of congenital myasthenic syndromes (CMS) related to pattern of inheritance and molecular targets at the neuromuscular junction

I. Pattern of inheritance	
Autosomal dominant (gain-of-function)	Slow-channel syndrome, SNAP25B*, SYT2*
Autosomal recessive (loss-of-function)	All other subtypes
II. Site of defect and molecular targets at the neuromuscular junction	
Presynaptic defects	ChAT deficiency, SNAP25B deficiency, synaptotagmin-2 deficiency
Acetylcholine receptor defects	Primary deficiency, slow-channel syndrome (CHRNA1, CHRNB, CHRND, CHRNE, CHRNG), fast-channel syndrome (CHRNA, CHRND, CHRNE)
Synaptic basal lamina defects	Acetylcholinesterase deficiency (ColQ), β2-laminin deficiency
Endplate development and maintenance congenital defects	Agrin deficiency, MuSK deficiency, LRP4 deficiency, Dok-7 deficiency, rapsyn deficiency, COL13A1 mutations
Metabolic and mitochondrial disorders	Congenital disorders of glycosylation, SLC25A1 gene mutations
Others	Congenital myopathies with secondary neuromuscular transmission compromise (MTM1, RYR1, DNM2, TPM3, BIN1); PREPL deletion; plectin deficiency

*Extremely rare presentations. ** This table is adapted from the study 'Clinical and Genetic Basis of Congenital Myasthenic Syndromes' by Souza P. et al.

syndrome, a condition whose incidence is primarily inferred from case reports.

Ethical approval

Since this is a case report, ethics committee approval was not required. Consent was obtained from the patient.

Author contribution

Surgical and Medical Practices: FB, SY; Concept: FB, SY; Design: FB, FE; Data Collection or Processing: FB, FE; Analysis or Interpretation: SY, FB, FE; Literature Search: SY, FB, FE; Writing: FB, FE. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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