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Late-diagnosed congenital myasthenic syndrome due to a CHRNE mutation: a case report

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Abstract

Congenital myasthenic syndromes (CMS) comprise a heterogeneous group of inherited disorders caused by genetic defects affecting neuromuscular junction transmission. Clinical manifestations range from isolated ocular symptoms to severe neonatal respiratory insufficiency. Despite symptom onset early in life, CMS is frequently underdiagnosed or misdiagnosed, most commonly as myasthenia gravis (MG), leading to prolonged diagnostic delay. We report a young woman with fluctuating muscle weakness and eyelid drooping since early childhood who had been followed for years with a diagnosis of seronegative MG. In adulthood, genetic analysis identified a homozygous nonsense mutation in the CHRNE gene, establishing the diagnosis of CMS. This case highlights the diagnostic challenges posed by CMS due to its clinical overlap with MG and emphasizes the critical role of genetic testing in patients with seronegative, treatment-resistant neuromuscular weakness.

Keywords: Congenital myasthenic syndrome, CHRNE, neuromuscular junction, seronegative myasthenia gravis, genetic diagnosis

INTRODUCTION

Congenital myasthenic syndromes (CMS) are rare inherited disorders caused by genetic defects in proteins required for neuromuscular transmission at the neuromuscular junction.[1-3] CMS is currently classified according to the site and molecular mechanism of the defect, including presynaptic, synaptic basal lamina-associated, and postsynaptic subtypes.[2,3]

Clinical manifestations range from neonatal hypotonia and respiratory insufficiency to isolated ocular or mild limb weakness, and symptoms may remain unrecognized until adolescence or adulthood.[4,5] This phenotypic variability frequently leads to diagnostic confusion with acquired neuromuscular disorders, particularly seronegative myasthenia gravis (MG), causing substantial diagnostic delay in adult patients.[5,6]

Among postsynaptic CMS, mutations in genes encoding acetylcholine receptor (AChR) subunits constitute a major etiological group. The CHRNE gene encodes the epsilon subunit of the AChR, which replaces the fetal gamma subunit after birth.[1,7] Pathogenic CHRNE variants are among the most frequent causes of CMS worldwide and have also been reported as an important CMS subtype in Turkish cohorts.[8-10] Loss of epsilon subunit function reduces endplate AChR density and impairs neuromuscular transmission. Because fluctuating weakness, ptosis, and ophthalmoparesis closely resemble MG, CHRNE-related CMS should be considered when antibody testing is negative and standard MG-directed treatments fail.[5,6]

CASE REPORT

A 22-year-old woman presented with childhood-onset ptosis and generalized muscle weakness that had worsened with exertion over the past three years. Symptoms began at approximately 2.5 years of age and included early fatigability, difficulty climbing stairs, and reduced physical endurance compared with peers, despite normal motor developmental milestones. She had previously been followed at another center with a diagnosis of seronegative myasthenia gravis. Serum anti-acetylcholine receptor and anti-MuSK antibodies were negative, and no clinical

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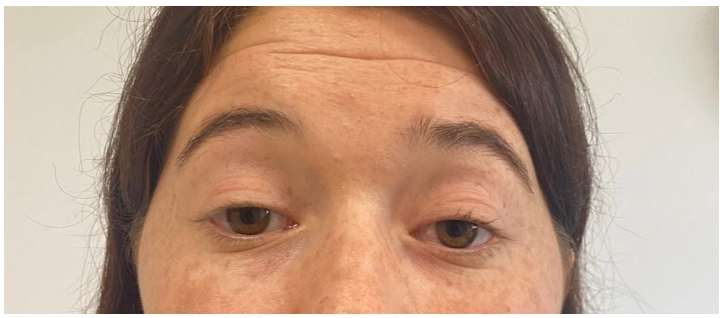

Figure 1. Bilateral ptosis observed on neurological examination.

response was observed with immunomodulatory therapies. Thoracic computed tomography revealed no thymic pathology. Neurological examination demonstrated bilateral marked ptosis (Figure 1), limitation of extraocular movements in all directions (Figure 2), and proximal muscle weakness graded as 4/5, with preserved deep tendon reflexes and normal sensory and cerebellar findings. Nerve conduction studies and repetitive nerve stimulation were normal, while serum creatine kinase level was mildly elevated (244 U/L). Genetic analysis identified a homozygous pathogenic nonsense mutation in the CHRNE gene (c.393C>G; p.Tyr131Ter), and segregation analysis confirmed heterozygous carrier status in both parents. The patient was diagnosed with CHRNE-related CMS. Salbutamol therapy was initiated, resulting in marked functional improvement at three-month follow-up.

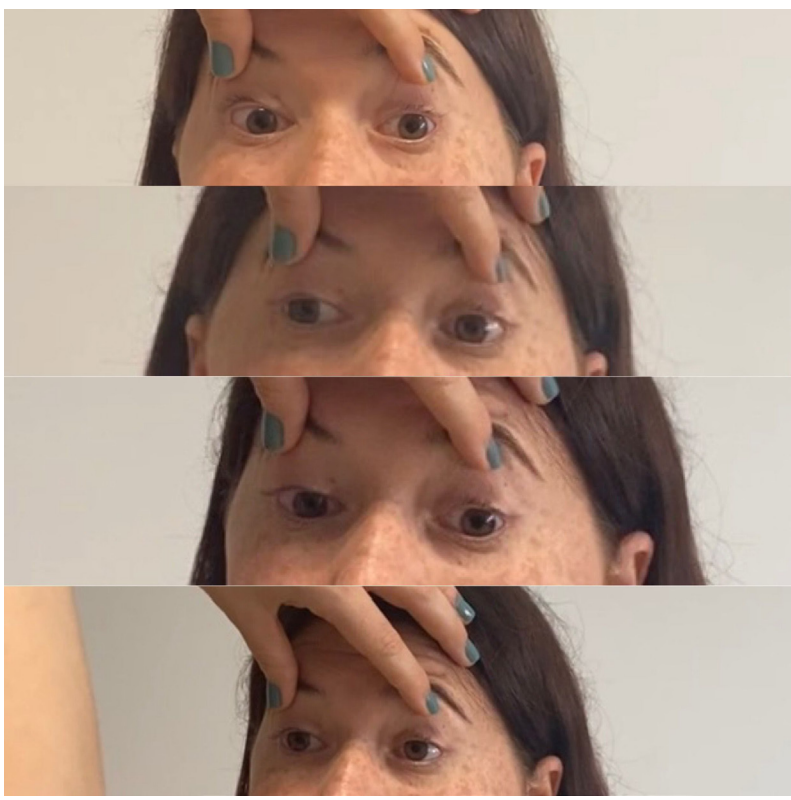

Figure 2. Limitation of extraocular movements in all directions, including leftward, rightward, downward, and upward gaze.

DISCUSSION

CMS constitute a diagnostically challenging group because of their marked clinical and genetic heterogeneity.[1,5] In our patient, the combination of childhood-onset ptosis, ophthalmoparesis, fluctuating proximal weakness, negative AChR/MuSK antibodies, absence of thymic pathology, and lack of response to immunomodulatory treatment argued against autoimmune MG and prompted genetic testing. Adult CMS cohorts show frequent initial misdiagnosis as seronegative MG and substantial diagnostic delays.[6]

The homozygous CHRNE c.393C>G (p.Tyr131Ter) nonsense variant identified in this patient is expected to cause loss of epsilon subunit function, leading to AChR deficiency and impaired neuromuscular transmission. CHRNE-related AChR deficiency is one of the most frequently reported postsynaptic CMS mechanisms.[7-10] A normal repetitive nerve stimulation study does not exclude CMS; therefore, genetic testing remains essential when the clinical picture is compatible.[5]

Therapy in CMS should be guided by the underlying genotype. For AChR epsilon-subunit deficiency, β2-adrenergic agonists such as albuterol/salbutamol and ephedrine have been associated with clinical benefit, and meta-analytic data support β2-agonist therapy in CHRNE-related CMS.[11-13] The marked improvement observed after salbutamol in our patient is therefore consistent with previous reports.

In conclusion, CMS due to CHRNE mutations may closely mimic MG and remain undiagnosed for years without genetic evaluation. CMS should be considered in patients with seronegative, treatment-resistant, childhood-onset, or fluctuating neuromuscular weakness. Early genetic diagnosis enables mutation-specific therapy and can substantially improve long-term functional outcomes.

DISCLOSURE

Ethics: Written informed consent was obtained from the patient for publication of this report.

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Conflict of interest: None.

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