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Case Report

De Novo CHRNE Mutation: Congenital Myasthenic Syndrome

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ABSTRACT

Congenital myasthenic syndromes (CMS) are neuromuscular hereditary diseases with the symptoms of fatigue, weakness, ptosis, ophthalmoparesis and respiratory problems. This disease group is classified as CMS originating from the presynaptic region, synaptic gap and postsynaptic region according to the origin of the neuromuscular junction. Most of these patients are affected by receptor defects originating from the postsynaptic gap. Here, we present a case who was thirteen years old and had a CHRNE genotype p.Y124 *(c.372C> G) homozygous mutation, which is associated with weakness, low voice, ophthalmoparesis and frequent respiratory infection since birth. Our patient has been diagnosed with non-kinetic AChR deficiency and the case is important with the detection of a new mutation.

Keywords: Acetylcholine receptor deficiency, congenital myasthenic syndrome

Introduction

Congenital myasthenic syndromes (CMS) are genetic disorders of the neuromuscular junction that can be clinically variable. Sometimes the same mutation can cause different clinics and sometimes different mutations can cause the same clinics. As of present, mutations identified as disease-related have been shown in only 50% of patients with clinically diagnosed CMD (1). Beginning in childhood, specific autoantibodies being negative, detection of decrement responses or M responses in patients instead of myopathy are the indications of CMS in the patient (2).

Clinical findings vary according to mutation. The most common mutations are the mutations that cause defects in acetylcholine receptors (AchR). The most frequently observed mutation in these is the CHRNE mutation (3,4). The identification of these mutations is important for avoiding pyridostigmine, which may worsen myasthenic syndromes such as COLQ, DOK7 and slow-channel syndrome (1). It is also important to predict the prognosis and the mutation of the existing disease is likely to lead to a life-threatening condition.

A patient who has CHRNE de nova mutation was presented. He can be classified in the group "AchR deficiency-without a kinetic abnormality" group or primary AchR deficiency group.

Case Report

A 13-year-old male born to a second-degree consanguineous marriage presented with complaints of low eyelid, low voice crying and frequent respiratory tract infections since birth (Figure 1, 2). He had been diagnosed as CMS from the age of 8 months and used

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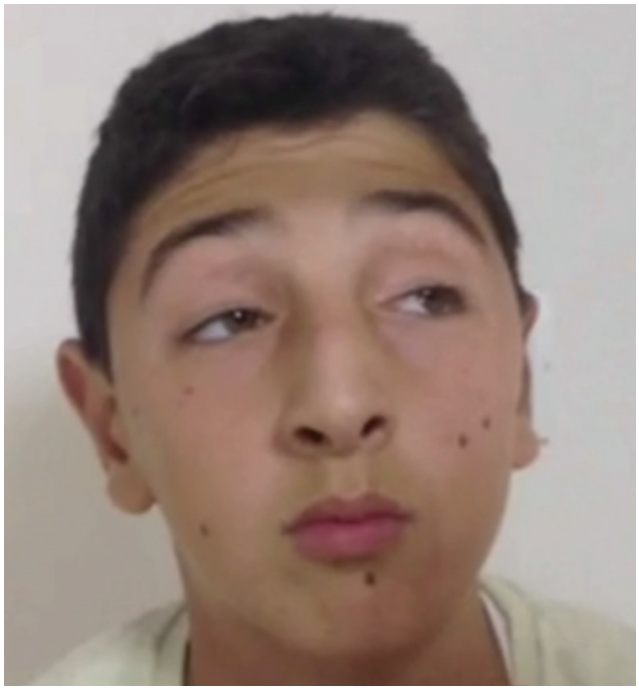

Figure 1. Bilateral ptosis

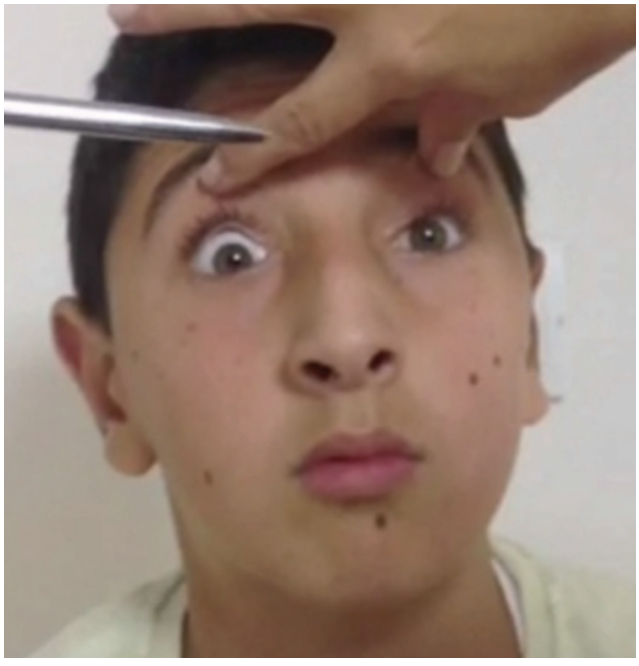

Figure 2. Bilateral ophthalmoparesis

pyridostigmine therapy and benefited. During this period, he had respiratory infections many times but he did not have a serious respiratory failure.

Neurologic examination revealed bilateral ptosis, outward and upward gaze limitation, thin and low voice, swallowing difficulty, normoactive deep tendon reflexes and 4/5 muscle strength. Skeletal anomaly and contracture were absent.

Muscle-specific tyrosine kinase and AChR antibody were negative. Electromyography (EMG) examination revealed 3 Hz decremental response at 3 and 5 Hz repetitive stimulation and there was no myopathy sign in needle EMG. Genetic analysis was performed for CMS, *de novo* p.Y124* (c.372C> G) homozygote mutation was also detected in the *CHRNE* gene. A mutation was not detected in the same region of the patient's parents. These findings were probable pathogenic for congenital myasthenic disease. The treatment of the patient continued with acetylcholine esterase inhibitors.

Informed consent was obtained from the patient's family.

Discussion

CMS, a hereditary disorder, is not characterized by autoimmunity. Lack of acetylcholine, kinetic anomalies, AchR deficiency, carrier protein anomalies or paucity of synaptic vesicle (2). Most complaints of patients start from birth. The defect may vary from severe respiratory failure to mild findings at birth, depending on the location (1-4). On physical examination, ptosis, limited eye movements, fatigable weakness, low crying, dysphagia and skeletal deformities can be observed (2). CMS are often misdiagnosed as congenital muscular dystrophies and mitochondrial myopathies because of their similar physical examination (1-4).

Weakness of diurnal rhythms in anamnesis, family history, recurrent infantile sibling death, frequent recurrent respiratory infections, age of onset of the disease and the progressive or stable course are helpful in diagnosing CMS.

For the diagnosis to be obtained in the decremental response in EMG, this response helps to narrow the differential recognition of presynaptic or post synaptic formation. Unlike autoimmune myasthenia in adult patients, repetitive stimulation for 5 minutes at 10 Hz in young children may be significant in terms of early and differential diagnosis (5). Even if CMS occurs clinically, genetic determination becomes important because of treatment differences.

In our patient, a postsynaptic decremental response was obtained, and this mutation was transmitted to the patient because the most common CMS in this group is associated with mutations in the *CHRNE* gene. Cases from our country showed that this mutation was detected in 15 of 43 patients (6).

Mutations in the *CHRNE* gene have been associated with CMS, which has a rapid channel kinetic abnormality and slow channel kinetic abnormality without AchR-kinetic abnormality (7-9).

However, consanguinity of the parents, the absence of similar disease histories in the family, and EMG findings excluded the autosomal dominant hereditary presynaptic region from the disease slow channel kinetic anomalies. The fast channel kinetic anomalies is a rapid and progressive disease. However, our patient's disease has been stable for years with only pyridostigmine treatment (2,4). Because of these, we thought that the fast channel kinetic anomalies was inappropriate for the diagnosis.

Consistent with the literature, our patient also had parents with a consanguineous marriage, stable clinical findings, intermittent swallowing difficulty and benefit from pyridostigmine (9-11).

With all these findings, our patient has complied with non-kinetic AChR deficiency and the case is important with the detection of a new mutation.

Since acetylcholine esterase inhibitors worsen the clinical condition in patients with mutations of DOK7, COLQ and slow-channel syndrome, differential diagnosis is very important in patients with CMS in order to conduct the correct therapy.

Although our patient responds to acetylcholine esterase inhibitors, in these cases 3-4-diaminopyridine and/or salbutamol may be tried in cases of treatment failure (1-3).

Ethics

Informed Consent: All of the parents of the patients gave their informed consent prior to their child's inclusion in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G., Concept: H.T., H.G.T., S.Y., Design: S.Y., H.G.T., Data Collection or Processing: G.A., H.G.T., Analysis or Interpretation: S.G., H.T., Literature Search: H.G.T., Writing: H.G.T.

Conflict of Interest: None of the authors had conflict of interest.

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