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Myotonic Dystrophy in a Female with Myasthenia Gravis

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The likelihood of coexistence in the same patient of myasthenia gravis and myotonic dystrophy has been estimated at 1 in 40 million. The case of a patient in whom both diagnoses were made is reported here. A 13-year-old girl was diagnosed with myasthenia gravis because of weakness, fluctuating fatigability, and mild difficulty with chewing and swallowing. She had ptosis, with weakness predominantly of her face, arms, and neck. Serum antibodies against acetylcholine receptors were 9.9 nmol/L. She was started on pyridostigmine, with significant clinical improvement, reassuming normal daily activities. Two years later, generalized weakness reappeared and reappraisal of her symptomatology disclosed tongue percussion and hand action myotonia. Molecular genetic analysis disclosed 550 repeats of cytosine-thymidine-guanosine triplets on the *DMPK* gene. Undiagnosed relatives had expansions ranging from 110 to 1000 repeats. Myotonic dystrophy is considered the most common muscular dystrophy, with highly variable clinical manifestations; mildly affected individuals may escape clinical detection. Myasthenia gravis has an estimated prevalence of 15 per 100,000. No studies on the epidemiology of these diseases have been done in Chile. Although both diseases have specific clinical and laboratory presentations, they share some features in the mode of presentation that may generate difficulty in diagnosis of both entities in the same patient.

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Introduction

Although myotonic dystrophy is considered to be the most common of the muscular dystrophies in the general population, the possibility of its coexistence in the same patient with myasthenia gravis due to chance has been estimated at 1 in 40 million [1]. Both diseases have specific clinical and laboratory presentations, but superficially share some features, which can preclude one diagnosis if the other is present. If the first diagnosis made is that of myasthenia gravis, there is a chance that all signs and symptoms are ascribed to this disease, making the concurrent diagnosis of myotonic dystrophy very difficult in the absence of family history or more specific complaints of myotonic dystrophy, as mental problems.

We present the case of such a patient, in whom diagnosis of a relative with myotonic dystrophy prompted a search for this second condition.

Case report

This girl was seen at age 13 years because of complaints of weakness and fatiguability predominantly in her arms, with daily and hourly fluctuations. Since age 11 she had noticed difficulty in participating in sports at school, especially when playing basketball, because of what she interpreted as fatigability of wrist extensors. At that time her symptoms were ascribed to psychogenic factors. She had no history of double vision or difficulty with eye opening or with swallowing.

At the time of her consultation she was a thin, well-developed girl, with above-normal intelligence. She had very mild ptosis, no oculomotor paresis, and a mildly nasal voice. There was generalized weakness, predominantly of her face, arms and neck flexors and extensors. She complained of mild difficulty with chewing and swallowing.

A diagnosis of myasthenia gravis was suspected and she underwent an edrophonium (Tensilon) test which resulted in definite improvement in strength in all muscles tested. Repetitive stimulation at low frequencies in median and ulnar nerves bilaterally yielded a decrementing response of >15%. Serum antibodies against acetylcholine receptors were found to be 9.9 nmol/L (normal range, <0.8 nmol/L) (Specialty Laboratories, Valencia, CA). Testing for striational antibodies yielded negative results (<1:40).

A diagnosis of autoimmune myasthenia gravis type IIB (Osserman) was made, and she was started on neostigmine and later on pyridostigmine, with partial but significant clinical improvement. She underwent thymectomy 6 months later, after which she progressively needed less of the anticholinesterase drugs and resumed normal daily activities. Pathology of the thymus showed no hyperplasia. She was maintained on low doses of pyridostigmine (60 mg three times daily) for the next 5 years, with almost no symptoms except a moderate facial weakness, until she had an episode of syncope followed by generalized weakness that required higher pyridostigmine dosing and admission to inpatient unit.

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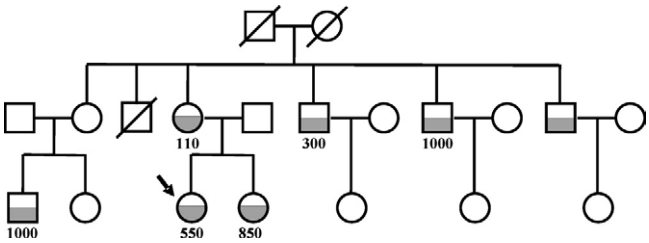

Figure 1. The family pedigree, indicating the number of CTG repeats in each case.

A first-degree cousin (consultation because of possible learning disorder) who was diagnosed with probable myotonic dystrophy led us to do a reappraisal of her symptomatology, which disclosed a mild tongue percussion and hand action myotonia which were also present in her mother, who didn't show or complain of weakness. Molecular genetic analysis [2], performed to determine the number of cytosine-thymidine-guanosine (CTG) triplets on the 3′ untranslated region of the *DMPK* gene in the index case, disclosed 550 repeats. Due to the presence of several other cases of probable myotonic dystrophy in the family, the same analysis was done in the relatives available. Figure 1 shows the family pedigree, indicating the number of CTG repeats in each case. As shown, all relatives presenting symptoms have an expansion of the repeats ranging from 110 to 1000.

Serum creatine kinase was within normal limits. Cardiac and endocrine evaluation disclosed no abnormalities. No cataracts were detected upon slit lamp examination.

Discussion

Clinical evidence and associated laboratory findings are consistent with the occurrence of both myasthenia gravis and myotonic dystrophy in this patient. This situation has been previously described in only four more cases in a bibliographic search. Schoen [3] described a 13-year-old girl who suffered from myotonic dystrophy who developed myasthenia gravis, and Maytal et al. [4] described a 16-year-old patient with ocular myasthenia whose mother and grandmother had myotonic dystrophy. Coexistence of myasthenia gravis with congenital myotonia has also been described [5], and so has myotonic dystrophy with thymoma and electromyographic findings consistent with myasthenia gravis [6]. More recently, a 61-year-old woman was found to have both disorders; myotonic dystrophy was confirmed by molecular assay, which detected an expansion of more than 50 repeats of trinucleotide CTG in locus 19q13.3 [1].

Myotonic dystrophy is considered to be the most common muscular dystrophy in the general population (estimated prevalence, 3 per 100,000), with mildly affected individuals escaping clinical detection. With the advent of molecular testing, a minimum prevalence rate of 9.31×10^{-5} inhabitants was found in Italy, much higher than estimates from previous studies conducted in the same areas but before molecular genetic testing was available [7]. Juvenile myasthenia is estimated to represent $<10\%$ of affected individuals in Western countries [8]. No studies on epidemiology of these diseases have been done in Chile.

The clinical presentation of acquired autoimmune myasthenia gravis comprises a pattern of weakness with characteristic distribution affecting ocular, facial, oropharyngeal, and limb muscles. There is fluctuation over the course of the day and over months or years, with worsening symptoms and remissions. Involvement of limb or respiratory muscles with concomitant sparing of ocular or oropharyngeal muscles is rarely if ever encountered.

Myotonic dystrophy type 1 has highly variable clinical manifestations. Patients may be asymptomatic, have minimal features (such as cataract or asymptomatic myotonia), show moderate or severe facial and distal limb muscle wasting and weakness, or have a severe congenital disorder [9]. It is due to an unstable trinucleotide repeat expansion containing cytosine-thymidine-guanosine [CTG]n, located in the 3′ untranslated region of chromosome 19q13.3 [2,10]. Analyses of DNA have demonstrated somatic mosaicism in some of the organs that show an increased incidence of symptoms: in comparison with leukocyte DNA, the length of the CTG repeat expansion is greater in skeletal muscle [11], brain [12], and heart [13].

The diagnosis of myasthenia gravis in the present case was confirmed by improvement of symptoms after intravenous administration of edrophonium chloride and a finding of decremental response to repetitive nerve stimulation and acetylcholine receptor antibodies in the serum. Although there are a few cases reported of positive responses to edrophonium in the absence of myasthenia gravis, practically no other disorder is associated with positive responses on edrophonium testing and acetylcholine receptor antibody studies. Acetylcholine receptor-binding antibodies are the first choice of assay for confirming a diagnosis of acquired myasthenia gravis [14]. A positive result is useful for distinguishing acquired myasthenia gravis (90% positive with generalized weakness) from congenital myasthenia gravis (negative).

Acetylcholine receptor-modulating antibody assay is advised when the acetylcholine receptor-binding antibody assay is negative, an occurrence more common in myasthenic children, or in adults with myasthenia gravis of recent onset (<1 year), of mild severity, or restricted to extraocular muscles or when thymoma is a consideration [15].

Although both diseases have specific clinical and laboratory presentations that permit appropriate diagnosis individually, they present with some common features that can make differentiation of the two diseases very difficult. Both can present with weakness with predominantly facial and hand/wrist involvement. Ptosis is more marked in myasthenia gravis, and has the unique characteristic of hourly fluctuations. This sign was not present in the

patient described here, and neither was diplopia, which partly explains the delay in the diagnosis and the erroneous assumption of a psychogenic origin for her first complaints. There were no specific symptoms of myotonic dystrophy, as face weakness could be ascribed to myasthenia gravis. As is usual, there was no complaint of myotonia, and no active search was done to exclude it during electrophysiological testing, because at the time there was no family or personal history alerting to the possibility of myotonic dystrophy.

This patient did not have symptoms or signs of sensory, upper motor neuron, or autonomic (central or peripheral) disease, nor difficulties with cognition or memory, which excludes myasthenia gravis—nor a positive family history of myasthenia gravis to bring into consideration one of the congenital myasthenic syndromes [16].

This patient demonstrates that even very rare diseases can occur in the same patient, sharing similar signs and symptoms, so even in the presence of a straightforward diagnosis a complete search for other conditions is necessary with a thorough follow-up.

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