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Oculopharyngeal muscular dystrophy as a cause of progression of weakness in antibody positive myasthenia gravis

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Abstract

Many neuromuscular conditions cause bulbar and limb weakness, and when several conditions coexist they present additional diagnostic challenges. Here we describe a case of a 45-year-old woman with antibody positive myasthenia gravis since age 16, who then develops treatment-resistant weakness due to genetically proven oculopharyngeal muscular dystrophy. We conclude that the development of treatment-resistant weakness in myasthenia gravis should spur further work up for other neuromuscular disorders including oculopharyngeal muscular dystrophy.

Introduction

Myasthenia Gravis (MG) with antibodies to the acetylcholine receptor is a common cause for bulbar and limb weakness. Acetylcholine esterase inhibitors combined with modern immunomodulatory treatments often control symptoms, both in the short and long term and in the majority of cases[1]. When treatments fail to maintain symptomatic control the cause can be either poor compliance, recurrence of an underlying thymoma, or a spontaneous worsening in the myasthenia disease process. Alternatively the development of a second condition such as a steroid myopathy, cholinergic crisis, or a new neuromuscular disorder such as thyroid orbitopathy, Guillain Barre syndrome, amyotrophic lateral sclerosis or polymyositis is possible [2-5]. To our knowledge oculopharyngeal muscular dystrophy (OPMD) has not been reported as a cause of progression of weakness in a case of antibody positive MG. Here we report a case of antibody positive MG and genetically proven OPMD followed for more than 30 years.

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Case Report

In 1979, a then 16-year-old woman presented with falls and limb weakness. She also reported occasional double vision, drooping eyelid, and a fair amount of neck weakness (Myasthenia Gravis Foundation of America class III). The symptoms were coming and going, clearly having a fatiguing quality. She had a positive edrophonium test and pyridostigmine and prednisone abolished her symptoms. A thymectomy was performed in 1979 and the thymus did not show any significant abnormalities. Her symptoms of weakness stayed quiescent and she was able to discontinue the prednisone and use only oral pyridostigmine as needed and infrequently.

In 1985 an acetylcholine receptor antibody was measured and found to be only marginally elevated at the time at 2 nmol/L (normal <0.1), and anti-striational antibodies were negative. Over the following 18 years her symptoms of weakness would periodically worsen and prednisone was added to the pyridostigmine on two occasions. The patient did not tolerate prednisone well, yet her symptoms of weakness would return to baseline and prednisone could be discontinued. On several occasions she had mild flares which dissipated without prednisone being introduced. Azathioprine was tried as an alternative to prednisone, but she developed leucopenia and the azathioprine was stopped.

In 2003 she became pregnant and suffered increased general and fluctuating fatigue during the pregnancy. She continued to use pyridostigmine monotherapy during the pregnancy. Her daughter was born at term, but was noted to be hypotonic and had respiratory insufficiency. The infant was intubated and treated for neonatal myasthenia gravis. After this initial acute illness the daughter has been a healthy young girl, without weakness to this date. After delivery the patient's acetylcholine receptor antibodies were markedly elevated (40.1 nmol/L, normal <0.02).

The patient improved clinically after the pregnancy, but needed to escalate the pyridostigmine to remain minimally symptomatic. She was not followed at the University clinic for the following five years. Over these following five years she developed a mild degree of fixed weakness that never resolved, but the majority of her symptoms remained fluctuating. The areas of fixed weakness were her eyelid levators, facial muscles, and proximal limb muscles.

When she returned to the University neuromuscular clinic in 2006 her exam was notable for mild ptosis, with otherwise intact extraocular muscles. She exhibited severe bilateral facial weakness and moderately weak accessory muscles. The muscle bulk was normal for both for facial and limb muscles. She had symmetrical weakness for the following movements: Shoulder abduction, flexion, and extension were all 4-/5; Elbow flexion was 4/5; Elbow extension was 4-/5; Grip, finger extension, and finger spread were 4/5; Hip flexion was 3/5; Knee extension and flexion were 2/5; Foot dorsiflexion was 3/5. Foot plantar flexion was 5/5. The patient could not stand out of a chair without the use of arms. She needed to use a Gower's maneuver to stand up from a squat. She was able to walk, but was unsteady, demonstrating a compensated Trendelenburg gait. The remainder of the neurological exam was normal.

An electrodiagnostic evaluation performed six hours after the patient's last dose of pyridostigmine, revealed significant decrement with slow repetitive nerve stimulation in three muscles, in particular, abductor pollices brevis 39%, trapezius 26%, and orbicularis oculi 32%. Electromyography revealed mild to moderate myopathic changes with brief, small amplitude motor unit action potentials recruiting early in the iliopsoas and in all tested cranial nerve innervated muscles. Chest imaging did not reveal any recurrence of thymic tissue. Creatine kinase was checked yearly over the three following years and ranged from 62-104 U/l (normal 24-195).

It was noted that the patient's family stems from the San Luis Valley in southern Colorado and that she is of Hispanic and native American heritage. She also had a family history of ptosis and some swallowing problems. Her deceased father late in life had developed marked ptosis and so did all but one of his seven siblings, including four brothers and two sisters. None of the siblings were known to have had limb weakness, but the youngest sisters had some swallowing problems.

We had her PABPN1 sequenced (encoding the polyadenylate binding protein nuclear 1) and one extended allele with 13 GCG repeats was found.

We concluded that the patient had both acetylcholine receptor antibody mediated MG and OPMD.

As her symptoms were fluctuating and helped by pyridostigmine we tried mycophenolate mofetil at 1g twice daily for one year as well as IVIG 2g/kg. Neither treatment resulted in any positive effect on her strength.

Discussion

This case illustrates the well established point that other diagnostic alternatives need to be kept in mind even after an initial diagnosis has been firmly established, if at a later time symptoms appears atypical. Myasthenia gravis alone certainly could have explained all the patient's symptoms, but the severe fixed weakness would have been unusual. The fixed symptoms suggested the possibility of an additional overlying disease, and in this case it was OPMD.

Oculopharyngeal muscular dystrophy is a disease which has a higher prevalence in both French Canadians and the early Hispanic population from the San Luis Valley of New Mexico and Colorado [6, 7]. OPMD is most frequently an autosomally dominantly inherited condition due to polyadenylate binding protein nuclear 1 GCG repeat expansion greater than 12. Rarely the disease is recessively inherited by individuals with intermediate triple repeat copy number of 11, rather than the normal copy number of 10. Other polyalanine coding codon repeats (GCA, GCT, GCC) cause similar diseases [8]. The most common repeat expansion in both South Western Hispanics and French Canadians is 13 GCG repeats, which is the number seen in our case.

The disease is characterized by progressive ptosis, followed by dysphagia and extraocular muscle weakness and later mild proximal limb weakness [7]. Onset is often in the fifth or

sixth decade and the disease is slowly progressive. The distribution of affected muscles largely overlaps with the muscles most prominently involved in MG. It is therefore noteworthy that in this patient both extraocular and pharyngeal muscles are less affected than the proximal limb muscles. This pattern of weakness was present without long term steroid use and no additional immunologic or other type of muscle disease was apparent. The myopathic changes seen on EMG were not irritative and a muscle biopsy seemed unlikely to reveal a third neuromuscular condition of significance. The two disorders present here are of different pathophysiological nature, but still could be connected. An increased risk of the development of MG has been postulated to occur due to muscle fiber degeneration in the setting of inherited myopathies and associated autoinflammation [9].

In most neurological cases parsimony provides the best clinico-pathological hypothesis and a combination of disorders is less common, but it can occur as illustrated here. A clinician should consider reevaluating a patient who is not progressing as predicted, and additional conditions may then be revealed.

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Abbreviations

MG	Myasthenia Gravis
OPMD	Oculopharyngeal muscular, dystrophy
IVIG	Intravenous immunoglobulin
EMG	Electromyography