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Atrophy and Fibrosis of Extra-Ocular Muscles in Anti-Acetylcholine Receptor Antibody Myasthenia Gravis

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Abstract

Myasthenia gravis (MG) is an autoimmune disorder involving the neuromuscular junction that frequently affects the extra-ocular muscles (EOMs). It has been described as a very rare cause of bilateral EOM atrophy, but histological analysis of such cases is lacking. A 66-year-old man presented with two months of right eyelid drooping and vertical diplopia. Examination showed bilateral ophthalmoparesis and complete right ptosis. The remainder of his exam was normal, and an MRI showed small EOMs. Acetylcholine receptor antibodies were elevated, establishing the diagnosis of MG. Oral corticosteroids and pyridostigmine followed by azathioprine improved his ptosis, but not his ophthalmoparesis. One year later he had surgical correction of his diplopia, and the resected superior rectus muscle showed complete replacement of EOM by connective tissue. MG can rarely cause bilateral EOM atrophy, which is characterized histologically by fibrosis in the muscle itself. Atrophy in the EOMs of a myasthenic patient may indicate a poor response to medical management alone.

Keywords

Myasthenia Gravis, Oculomotor Muscles, Muscular Atrophy

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction most often caused by autoantibodies targeting the post-synaptic acetylcholine receptor (AChR). While the primary site of pathology in MG is the neuromuscular junction, muscle changes also occur. Lymphocyte infiltrates and muscle fiber atrophy are

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the most commonly described changes in the muscle of patients with MG [1]-[4]. While modern diagnostic techniques have made muscle biopsy obsolete in the diagnosis of MG, an understanding of the spectrum of muscle pathology in MG can still be pertinent to clinical practice. We present a case of anti-AChR antibody positive myasthenia gravis with atrophic and fibrotic extra-ocular muscles (EOMs) who had a poor response to medical therapy.

2. Case Report

A 66-year-old man presented with two months of right eyelid drooping and vertical binocular diplopia, both worse in the evening. Examination showed almost complete ophthalmoplegia of the right eye. The left eye also had limited abduction and depression. He had complete right upper lid ptosis. Digital forced ductions were normal indicating no mechanical restriction in moving the eye upwards. His pupils were 4.5 mm and equally reactive. The remainder of his exam was normal.

MRI showed uniformly small EOMs in both eyes (**Figure 1**). An intravenous edrophonium test was deferred due to elevated blood pressure (194/107). Serum AChR-binding antibodies were found to be elevated; therefore a diagnosis of myasthenia gravis was made.

The patient was treated with oral corticosteroids and pyridostigmine, followed by the addition of azathioprine. While his ptosis improved, he continued to have constant diplopia. One year later he opted for surgical correction of the diplopia. The resected superior rectus muscle specimen was sent for histopathological analysis. H&E stain showed fibrocellular material replacing muscle tissue, and modified trichrome stain revealed near-complete replacement of muscle by connective tissue (**Figure 2**). This was later confirmed using other stains such as desmin. There were no ragged red fibers.

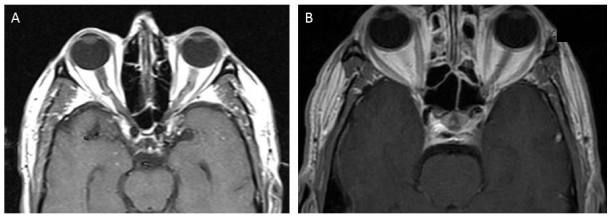

Figure 1. MRI brain of patient and control. (A) T1 axial post-gadolinium MR image of our patient at presentation showing uniformly atrophic extra-ocular muscles; (B) T1 axial post-gadolinium MR image of a healthy age-matched control patient to serve as a comparison for extra-ocular muscle size.

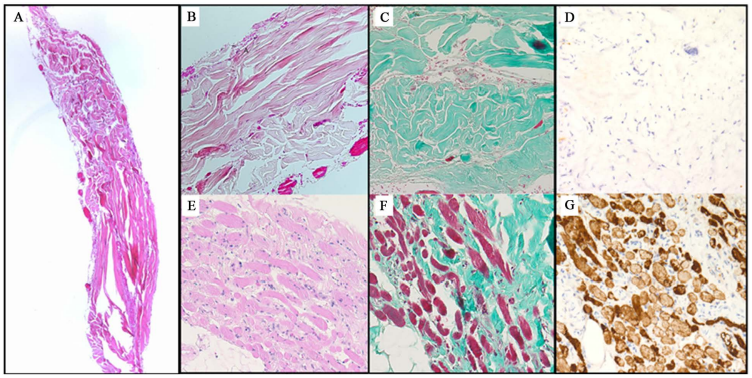

Figure 2. Extra-ocular muscle histopathology from patient ((A) 4× magnification; (B)-(D) 20× magnification and control; (E)-(G) 20× magnification). (A) Low-power H & E stain of the superior rectus muscle specimen showing fibrocellular tissue; (B) H & E stain at higher power showing fibrocellular tissue; (C) Modified trichrome stain showing near complete absence of muscle tissue replaced by collagen and no ragged red fibers; (D) Desmin stain with only trace staining consistent with absence of muscle tissue; (E) H & E stain of control muscle showing normal EOM fibers; (F) Modified trichrome highlights collagen around muscle fibers; (G) Desmin stain highlights muscular tissue.

3. Discussion

Bilateral EOM atrophy is a rare entity that has been described in mitochondrial myopathies, myotonic dystrophy, and congenital fibrosis syndromes [5]. MG has also been reported as an extremely rare cause of such atrophy. In a case series of seven patients with bilateral EOM atrophy, three patients had MG while the remainder had mitochondrial myopathies. One of the patients with MG in this series had anti-AChR antibodies [6]. Chan and Orrison reported the case of a 49-year-old man with anti-MuSK antibody positive MG who also had "severe wasting" of EOMs bilaterally [5]. All four of these MG patients with EOM atrophy received appropriate treatment, but none had significant improvement.

In the early part of the 20th century, muscle biopsy was used as an aid to the diagnosis of myasthenia gravis. In 1953, Russell published a landmark paper describing muscle findings in MG, including inflammatory changes and simple fiber atrophy [1]. In subsequent years, others would elaborate on these findings. Notably, Fenichel reported that the simple fiber atrophy described by Russell occurred in a "grouped" fashion, typical of denervation. The presence of both denervation changes and inflammation in the muscle itself led Fenichel to surmise that "the possibility that myasthenia may be a syndrome secondary to a primary abnormality on either side of the synapse is real" [2]. We now know that the primary abnormality in MG localizes to the synapse itself. Antibody-mediated inflammation leads to lymphocytic infiltration of the neuromuscular junction and surrounding tissue. Eventually the inflammatory response so damages motor endplates that the muscle is effectively denervated, resulting in atrophy.

Given the evolution of our knowledge about MG, and in particular the discovery of pathogenic autoantibodies in the disease, muscle biopsy is no longer performed as an aide to its diagnosis. Because our patient opted to undergo strabismus surgery, we had the unique opportunity to perform a histological examination of the affected muscle. To our knowledge this is the first report of histopathology in a patient with MG and EOM atrophy. This examination revealed abundant collagen deposition consistent with fibrosis that essentially replaced all of the muscle tissue. This fibrosis is consistent with a chronic process, most likely from chronic inflammation at the neuromuscular junction that has subsequently become dormant due to the absence of healthy AChR to serve as an autoantigen.

As was the case in the four previously reported patients with MG and EOM atrophy, our patient had a poor response to medical treatment. The histological findings in our patient provide a straightforward explanation for these outcomes: there simply isn't enough functioning EOM tissue left to effect muscle contraction even with appropriate treatment. Because of these findings, the clinician should be aware that MG can cause bilateral EOM atrophy, and that the presence of atrophic EOMs may portend a worse prognosis to medical therapy.

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