When Facioscapulohumeral dystrophy Meets Myasthenia gravis: Case Report and Literature Review

Arsh Ketabforoush MD[1,2*], Ryan Castoro MD[1,2], W. David Arnold MD[1,2,3,4], Richard J. Barohn MD[1,3]

[1] NextGen Precision Health, University of Missouri, Columbia, Missouri , USA
[2] Department of Physical Medicine and Rehabilitation, University of Missouri, Columbia, Missouri , USA
[3] Department of Neurology, University of Missouri, Columbia, Missouri , USA
[4] Department of Medical Pharmacology and Physiology, University of Missouri, Columbia, Missouri , USA

ABSTRACT

Simultaneous occurrences of rare disorders are significant diagnostic and management challenges. In this case report, we describe the initial clinical presentation, diagnosis, and management of a 66-year-old man with a history of concurrent facioscapulohumeral dystrophy (FSHD) and myasthenia gravis (MG). He presented at age of 54 with longstanding symptoms of facial, scapular, and limb weakness which was previously diagnosed at age 23 as limb girdle muscular dystrophy. He also exhibited new symptoms of ptosis, diplopia, and bulbar muscle weakness. Genetic testing and acetylcholine receptor autoantibody testing confirmed the diagnoses of both FSHD and MG. This report discusses the diagnostic obstacles, findings before and after treatment, and reviews previously reported cases of concurrent FSHD and MG. We emphasize the need for clinicians to remain vigilant for the development of symptoms from another rare disease in patients already diagnosed with one, avoiding premature attribution of new symptoms to the baseline condition.

Introduction

Facioscapulohumeral dystrophy (FSHD) is the third most prevalent type of muscular dystrophy, following Duchenne muscular dystrophy and myotonic dystrophy type 1.[1] The pooled prevalence of FSHD across all age groups is 3.95 per 100,000 individuals.[2] FSHD is primarily inherited as an autosomal dominant disorder, though up to 30% of cases occur sporadically due to de novo mutations. Symptoms of FSHD generally manifest in the second decade of life but can appear at any age, ranging from infancy to late adulthood.[3] Clinically, FSHD presents with asymmetric, gradually progressing weakness that initially affects the face, shoulders, and arms. This is followed by the distal lower limbs and pelvic girdle muscles involvement. Bulbar, extraocular, and respiratory muscles are often not affected.[4]

Myasthenia gravis (MG) is an autoimmune neuromuscular junction disorder marked by fatigue and weakness of skeletal muscles with a global prevalence of approximately 12.4 per 100,000.[5,6] In MG, autoantibodies target acetylcholine receptors or associated proteins in the pre- and post -synaptic membranes of the neuromuscular junction or the synaptic space. These autoantibodies cause variable localized or generalized skeletal muscle weakness. The weakness predominantly affects proximal muscles more than distal ones and almost always involves the extraocular muscles, leading to diplopia and ptosis.[5]

The simultaneous occurrence of FSHD and MG is uncommon according to medical literature and poses significant diagnostic and management challenges. Through the presentation of a rare case of concurrent MG and FSHD combined with a review of the literature we outline the complicated clinical presentation and immunomodulation responses for this unique population.

Case Presentation

The patient is a 66-year-old male who was initially seen at 54 years of age. At that time, he presented with chronic symptoms of limb weakness with prominent scapular winging. When he was 19 years old he developed proximal arm weakness and was diagnosed with an unspecified limb-girdle muscular dystrophy after a muscle biopsy at 23 years of age. Similar symptoms were reported in his mother, maternal grandmother, and sister, and he mentioned that his sister had a positive genetic test for "muscular dystrophy" and also had MG. She lives in California, and we are not able to obtain her records. Despite the patient's symptoms, he was active and worked as a police officer. When he was 54 years old, he developed new, variable symptoms of diplopia, ptosis, and worsening difficulty with chewing. Given the insidious onset of his bulbar symptoms, an MG workup was done, and he was diagnosed with the condition. Serologic testing revealed a positive ACh-R antibody (we do not have the level from that time), and genetic testing reveled a contraction of D4Z4 repetitive element on chromosome 4q35 consistent with FSHD type I.

Over the next decade he was been treated with a variety of medications for MG at various times, including pyridostigmine, prednisone, mycophenolate mofetil, and intravenous immunoglobulin (IVIG). Over nine years he had two episodes of exacerbation and was hospitalized for plasmapheresis, with one resulting in temporary mechanical ventilation. Ultimately, chronic monthly IVIG treatment was very effective, and he tapered off prednisone and mycophenolate mofetil. ACh-R antibody titer was 10.4 ng/L four years after diagnosis. Two years ago, his insurance company denied continued IVIG treatment. Since then,

Table 1. Motor examination results are graded from 0 (no contraction) to 5 (normal strength) for both the right and left sides across various muscle groups tested.

Muscle	Right	Left	Muscle	Right	Left
Orbicularis oculi	3	3	Knee Extension	5	5
Orbicularis oris	3	3	Knee Flexion	5	5
Neck Flexion	4		Ankle Dorsiflexion	4	4
Neck Extension	5		Ankle Plantarflexion	5	5
Shoulder Abduction	4+	4+	Ankle Eversion	4+	4+
Elbow Flexion	5-	5-	Ankle Inversion	5	5
Elbow Extension	5-	5-	Hip Flexion	4	4
Wrist Flexion	5	5	Hip Abduction	5-	5-
Wrist Extension	5	5	Hip Adduction	5	5
Finger Abduction	5	5			
Finger Extension	4+	4+			
Thumb Abduction	4	4			

he has been maintained on pyridostigmine, but he has experienced cholinergic side effects, which have limited its use. He has been offered complement inhibitor and Fc blocker medication, but he has declined. He continues to report ongoing symptoms, but he is willing to tolerate his current symptoms without restarting prior medications or starting new medications. At his most recent follow up visit, he reported experiencing occasional ptosis, double vision, and difficulty in chewing and swallowing. The Myasthenia Gravis Activities of Daily Living (MG ADL), with a score of 6, scoring 1 on following parameters: chewing, swallowing, breathing, rising from a chair, double vision, and eye droop.[7] On examination, there was bilateral scapular winging. Extraocular motility was full and there was no ptosis. The right and left eye had a palpebral fissure measurement of 10 mm. The motor examination results are summarized in Table 1. His most recent serum AchR antibody level was 3.56 nm/L.

Discussion

Both FSHD and MG are rare diseases, and their coexistence has seldom been reported. *Table 2* provides a concise summary of cases reporting concurrent occurrences of both MG and FSHD.[8,9] One of the authors (RJB) reported two cases in 2004 with Italian colleagues.[10] Prior to this publication the most recent cases were reported in 2019. Filippeli et al. reported a 69-year-old woman with a 13-year history of FSHD, confirmed by a DNA deletion test, who presented with dysphagia, diffuse limb weakness, and binocular diplopia. The diagnosis of MG was confirmed through a decrement response on repetitive nerve stimulation, increased jitter values in single-fiber electromyography, elevated acetylcholine receptor-binding antibodies, and significant improvement following pyridostigmine and IVIG therapy.[11] Also in 2019, Nauman et al. reported a 77-year-old patient with a confirmed diagnosis of FSHD for 27 years and MG for 4 years, who experienced worsening symptoms such as double vision, ptosis, swallowing difficulties, and exacerbation of previous weaknesses. Following treatment with IVIG, the patient's condition notably improved.[12] The first reported case in the literature was by Sakuma et al. when described a similar case involving a 50-year-old man with a 35-year history of FSHD who developed MG.[13] The primary lesson from these reports is that the onset of bulbar and extraocular symptoms in a patient with established FSHD should raise suspicion for MG and prompt further evaluations such as repetitive nerve stimulation, single-fiber EMG, and antibody titer detection.

Could there be secondary mechanisms which MG and FSHD are related? AChR antibodies have been observed in patients with various other diseases, including myotonic dystrophy, limb-girdle muscular dystrophy, and mitochondrial myopathy and ALS.[14-16] The detection of AChR antibodies indicates a breakdown of immune tolerance to these receptors, likely due to muscle fiber degeneration and subsequent autoinflammation.[15] Minor alterations in the structure of the AChR within skeletal muscle due to degenerative processes could potentially trigger sensitization. This, along with the release of DNA or RNA particles from degenerating muscle tissue, might activate Toll-like receptors (TLRs), responsible for responding to inflammatory signals from both pathogens and internal cellular damage. These modified antigens may then activate CD4 cells and B cells. If the immune system detects significant changes in these antigens, tolerance could be disrupted, leading to the production of autoantibodies.[15]

Moreover, in FSHD as many as 80% of muscle biopsies from patients display some level of infiltration by mononuclear inflammatory cells. However, despite this infiltration, disease progression remains unaffected, and patients do not experience any benefits from prednisone treatment.[9,10] Therefore, in cases where both FSHD and MG occur simultaneously, the detection of AChR antibodies

could be an indication of the immune-mediated process triggered by underlying muscle damage due to muscular dystrophy. Perhaps this could explain why our patient's sister also may had FSHD and MG. Based on the prevalence rates of 3.95 per 100,000 for FSHD and 12.4 per 100,000 for MG and the world population is 8,115,094,06015 (as of 2024) while ignoring the biases of meta-analyses, it is estimated that approximately 40 people worldwide are experiencing both conditions concurrently.

Our patient exhibited symptoms of FSHD approximately 30 years before being diagnosed with MG, similar to the case of Asadollahi et al. the other cases MG developed several years after FSHD diagnosis.[8-13] In a patient with FSHD the following should raise the suspicion of MG: double vision, new asymmetric ptosis, new acute or subacute difficulty with chewing and swallowing, and acute respiratory failure.

Our literature review indicates that most of the reported cases of concurrent FSHD and MG occur in men and diagnosed after the fifth decade of life.[8-10,12,13] In some instances, the FSHD diagnosis was initially missed and only identified later when significant FSHD symptoms, such as foot drop, became evident.[8,9,13] In terms of treatment despite the underlying weakness from FSHD the symptoms of MG responds to standard treatment of MG including pyridostigmine, corticosteroids, and intravenous immunoglobulin (IVIG).[8-13]

Often, physicians may prematurely attribute new symptoms to the baseline rare disease the patient is already experiencing (i.e. Occam's razor). Thus, a lesson of this report is that clinicians should recognize that a patient with one rare disease can develop symptoms of another rare disease. This reinforces the famous quote from Sherlock Holmes: "When you have eliminated the impossible, whatever remains, however improbable, must be the truth".[17]

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Table 2. Summary of cases reporting concurrent occurrences of both MG and FSHD.

	Cases							
Author	Ketabforoush et al.	Filippelli et al.[11]	Nauman et al.[12]	Asadollahi et al.[8]	Sansone et al.[10]	Sansone et al.[10]	McGonigal et al.[9]	Sakuma et al.[13]
Year	2024	2019	2019	2012	2004	2004	2002	2001
Country	USA	Italy	USA	Iran	Italy-USA	Italy-USA	UK	Japon
Age	66	69	77	70	69	60	56	50
Sex	Male	Female	Male	Male	Male	Male	Male	Male
FSHD manifestation	FSHD symptoms began at age 19. MG symptoms and the FSHD diagnosis occurred at age 54.	diagnosed with FSHD 13 years prior	diagnosed with FSHD at the age of 50 (27 years ago)	50-year history of slowly progressive asymmetrical weakness of proximal upper limb muscles.	clinically diagnosed with FSHD, confirmed by deletion analysis (33 kb) two years prior to admission	For 5-10 years, there has been mild, fluctuating difficulty in raising arms overhead, carrying heavy items, and standing up straight.	nearly 40-year history of foot drop and shoulder girdle weakness	35-year history of FSHD affecting the lower extremities
Family history of FSHD	Sister, mother, and maternal grandmother	two brothers and one nephew						Mother
MG manifestation	diplopia, ptosis, and worsening difficulty with chewing	20 days history of nasal timbre, followed by dysphagia and diffuse limb weakness needing bilateral support for walking, with binocular diplopia on the vertical plane appearing in the last 10 days	Diagnosed with MG at age 74 (3 years ago), his symptoms worsened, including double vision, ptosis, and swallowing issues, along with the deterioration of previous weaknesses.	15 days history of progressively worsening difficulty in chewing and dysarthria	sudden onset of dyspnea, dysphagia, dysarthria, ptosis, and severe limb weakness	fluctuating dysarthria that began 8 months prior	4 months history of left eyelid drooping, varying in severity throughout the day	Difficulty in chewing and swallowing
Anti acetylcholine receptor antibody	10.4 nmol/L	16.01 nmol/l	elevated	markedly elevated	12 pmol/L	4.1 pmol/L	6.71 nmoles/L	97 nmol/L
Repetitive nerve stimulation (RNS)		(− 10.8% at 2 Hz, − 15.6% at 5 Hz) on the orbicularis oculi muscle and (− 14.9% at 2 Hz, − 15.2% at 5 Hz) trapezius		decrement response	decremental response	decremental response	Normal Limits	waning pattern

SFEMG/EMG		Myopathy-increased jitter in the extensor digitorum communis (in 65%of 20 pairs, mean value 55.8 us)		myopathy		short-duration motor unit potentials	SFEMG showed increased jitter (mean 72.3 microseconds)-EMG demonstrated short duration polyphasic motor units with a high frequency recruitment pattern, indicating a myopathic process.	myopathic changes
Edrophonium Test		Neostigmine test was performed. Dysarthria, ptosis, and diplopia showed dramatic improvement, with returning of RNS to normal after 25 min from neostigmine injection (− 9.6% at 5 Hz		dysarthria and chewing difficulty showed dramatic improvement			ptosis improved with edrophonium	decreased waning and the clinical symptoms
Thymoma		not detected	not detected				small thymoma-Thymectomy	thymectomy
creatine kinase		high (414 UI/l)	elevated	normal		1.5-fold elevation		normal
Treatment	Chronic intravenous immunoglobulin (IVIG), pyridostigmine	intravenous immunoglobulin (IVIG) therapy at 0.4 g/kg/day for 5 days and started on pyridostigmine	steroids, pyridostigmine, and mycophenolate mofetil-IVIG treatment at 1g/kg/day for 2 days.	choline-esterase inhibitor agents	dexamethasone (25 mg daily), azathioprine (50 mg daily), and pyridostigmine (270 mg daily)	Pyridostigmine-mycophenolate mofetil (1000 mg twice daily)	pyridostigmine	corticosteroid and choline esterase inhibitor