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Frequent Co-occurrence of AChR-Positive Myasthenia Gravis in Facioscapulohumeral Muscular Dystrophy Suggests a Novel Disease Association

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Abstract

Background:

Facioscapulohumeral muscular dystrophy (FSHD) is a genetic myopathy caused by inappropriate expression of the DUX4 gene. Myasthenia gravis (MG) is an autoimmune disorder targeting the neuromuscular junction, usually via anti-acetylcholine receptor (AChR) antibodies. Both conditions are rare, though isolated reports describe their co-occurrence. We aimed to determine whether the frequency of co-existing FSHD and MG exceeds chance expectation.

Methods:

We conducted a retrospective observational study across UK MG clinics. Genetically confirmed FSHD cases with AChR antibody-positive MG were identified through clinician report and historical review. Clinical data were extracted where available, including age of onset, antibody titres, thymic findings, and D4Z4 repeat size.

Results:

13 cases of dual FSHD and MG were identified, of which 9 were living. Based on prevalence estimates (FSHD 12/100,000, MG 20/100,000), only 1.6 cases would be expected in the UK by chance; our findings represent a 5-fold increase (95% CI: 2.6–10.7; p = 0.000045). Detailed data were available for 10 patients: 7 were male, median age of MG onset was 55.5 years (range 30–75). MG onset followed FSHD in 8/10 (mean interval 14.9 years). All tested patients had genetically confirmed FSHD1 and positive AChR antibodies. Thymic pathology was identified in only one patient.

Conclusion:

The observed frequency of MG in FSHD patients exceeds chance expectation, suggesting a novel disease association. DUX4 is aberrantly expressed in thymus and muscle in FSHD, and may predispose to MG. Clinicians should consider MG in atypical FSHD presentations. Further studies are warranted to explore this association.

Facioscapulohumeral muscular dystrophy (FSHD) is a common inherited muscle disorder (prevalence 5–12/100,000) caused by epigenetic de-repression of the normally silenced DUX4 gene[1]. It produces progressive weakness of facial, shoulder girdle and later limb muscles, with no current targeted therapy. Myasthenia gravis (MG), in contrast, is an autoimmune neuromuscular junction disorder most often due to anti-acetylcholine receptor (AChR) antibodies, causing fatigable weakness that typically affects extraocular, bulbar, respiratory and proximal limb muscles. MG is treatable but requires timely recognition to prevent life-threatening crises

and has a UK prevalence of 10–20/100,000 [2]. Although both conditions are rare, several reports describe their co-occurrence. FSHD is associated with inflammatory changes in skeletal muscle, and DUX4 is expressed in the thymus, an organ central to T-cell tolerance [3]. This pilot study therefore aimed to determine whether MG occurs more frequently in FSHD, and to explore whether FSHD may predispose to AChR autoimmunity.

Methods:
We conducted a retrospective multicentre study across 12 UK MG specialist centres. Patients with both MG and genetically confirmed FSHD were identified through the UK MG database and direct clinician reporting. For deceased individuals not included in the registry, next-of-kin consent was obtained before data extraction. Centres provided estimates of the populations they served, enabling calculation of local FSHD populations using prevalence of 12 per 100,000; MG prevalence within FSHD cohorts was then derived for each site. Available demographic and clinical data included age of onset for both conditions, sex, D4Z4 repeat length, AChR antibody titres, thymic imaging findings and thymoma status, MG pattern, Osserman classification, presenting features, and treatment response. To determine whether the observed co-occurrence exceeded chance expectation, we performed a one-sample Poisson test comparing observed and expected case numbers based on published UK prevalence estimates.

Results:
Using upper-bound prevalence estimates for MG and FSHD (FSHD 12/100,000, MG 20/100,000), the expected co-occurrence in the UK population would be approximately 1.6 individuals. We identified 9 living patients with both genetically confirmed FSHD and AChR antibody-positive MG, yielding an observed-to-expected ratio of 5.6 (95% CI: 2.6–10.7). This excess is statistically significant ($p = 0.000045$, Poisson exact test), strongly supporting a non-random association. An additional 4 patients who had died within the past 10 years and who met the same criteria were identified. Data were collected from 12 MG specialist centres across the UK. Of these, 10 centres reported having treated at least one patient with both FSHD and MG, and 8 centres reported at least one currently prevalent case. Estimates of the FSHD population served by each clinic ranged from 1 per 60 to 1 per 720. Correspondingly, the mean frequency of MG among FSHD patients from these 7 centres was 1 in 252, (range 1 in 60 to 1 in 720) - markedly higher than the general population prevalence of MG, estimated at 1 in 5,000. After adjusting for the higher prevalence of MG in older men (expected 1.37 cases), the observation of six male cases ≥40 remained significantly above chance (Poisson $p=0.0029$).

All cases had genetically confirmed FSHD1 with D4Z4 repeat contraction within the pathogenic range. Two of the cases were from a single family. Detailed clinical data were available for 10 patients. 7 cases were male. MG onset followed the onset of FSHD symptoms in 8 of 10 cases, with a mean interval of 14.9 years (range 1–33). Clues which prompted consideration of MG diagnosis included bulbar involvement, ptosis and ophthalmoplegia. In 2 cases, MG was diagnosed before or simultaneously with FSHD; in these cases the duration of FSHD symptom onset was unclear due to clinical overlap. All cases had positive AChR antibodies. One patient had thymoma; in the remaining cases, CT imaging revealed normal thymic anatomy. All cases demonstrated clinical response to pyridostigmine and/or immunosuppression.

Discussion:

The observed frequency of co-occurring FSHD and AChR antibody-positive MG in our cohort is significantly higher than expected by chance, suggesting a biological association. This has important clinical implications. MG is highly treatable and should be considered in FSHD patients with atypical features, disproportionate weakness for D4Z4 repeat size, or subacute decline. Overlapping facial, respiratory and proximal limb weakness could complicate diagnosis, and timely recognition is critical, as untreated MG may progress to bulbar or respiratory crisis and be mistaken for FSHD progression. Ocular involvement was absent in 4 of 10 cases, underscoring the need for vigilance for subtle MG presentations.

We speculate about biological pathways underlying this association. DUX4 encodes a transcription factor with potent immunomodulatory effects. Aberrant DUX4 expression in skeletal muscle drives degeneration with inflammatory infiltrates and MHC class I upregulation[4]. In cancer biology, constitutive DUX4 expression alters innate and adaptive immunity by inhibiting interferon pathways, and suppressing IFN-γ-induced STAT1 transcription - mechanisms relevant to immune evasion [5]. Disruption of STAT1-regulated thymic promoters has

also been implicated in early-onset and thymoma-associated MG, where impaired AIRE (autoimmune regulator) -mediated transcription results in loss of tolerance to the AChR. Notably, DUX4 is expressed in the adult human thymus, although its physiological role there is unknown[3]. Aberrant thymic expression may impair central tolerance and promote AChR autoimmunity. Alternatively, chronic inflammation and regenerative stress in FSHD muscle could create a peripheral environment that favours immunisation against muscle antigens.

To our knowledge, no prior publications have systematically identified cases of MG in individuals with FSHD or examined population-level co-occurrence. Although our study is an initial and necessarily limited exploration, the markedly increased incidence of MG in FSHD remains compelling, even under conservative prevalence assumptions. Limitations include the small sample size, retrospective design, incomplete clinical data, and potential referral or reporting bias particularly as referral of complex cases to specialist centres may have disproportionately increased identification of coexisting MG and FSHD. Nonetheless, the consistency of findings across multiple, geographically diverse centres supports a genuine association.

Conclusion:

We report a fivefold higher than expected co-occurrence of MG in patients with genetically confirmed FSHD, raising important clinical and biological questions. Neurologists should be alert to MG in FSHD patients with atypical or rapidly progressive features, and to possible FSHD in treatment-refractory MG. Larger prospective studies are required to verify the association and determine true prevalence. Investigating how aberrant transcriptional regulation in FSHD affects thymic and skeletal muscle immune pathways may provide insight into mechanisms predisposing to autoimmunity.

Estimated total population served by clinic (million)	**Estimated FSHD population served by clinic**	**Age (decade); Sex**	**FSHD age of onset (decade)**	**D4Z4 repeat length**	**MG age of onset**	**MG pattern**	**AChR ab status; Titre nmol/L**	**Treatment; Response**
6	720	40s; M	30s	7	40	Ocular and proximal limb	Positive; 21.4	Pyrido, thymectomy; Limited response
5.8	696	50s; F	40s	5	52	Ocular, bulbar	Positive; titre not known	IVIg, MMF; Improvement.
2	240	70s; F	40s	4	62	Bulbar, neck and limb	Positive; 0.64	Pyrido; Improvement
2	240	50s; M	40s	4	41	Bulbar and limb	Positive; 19	Pred, Aza; Improvement
2	*240*	*70s; M*	*70s*	*6*	*64*	*Bulbar, ocular and respiratory*	*Positive; 16*	*Pred, pyrido, Aza; Improvement.*
2	*240*	*80s; M*	*60s*	*8*	*59*	*Bulbar, upper limb*	*Positive; 10*	*Pred, pyrido, MMF; Improvement.*
0.8	96	54; M	Teens	4	50	Generalised	Positive, 14.7	Pred, pyrido, zilucoplan, ritux; Improvement
1.8	*216*	*80s; M*	*50s*	*6*	*75*	*Generalised*	*Positive; >20*	*Pred, pyrido, IVIg; Improvement*

0.5	60	70s; F	30s	NK	62	Generalised	Positive; titre not known	Pred, pyrido, Aza; Improvement
3.5	420	30s; M	20s	7	30	Generalised	Positive; >20	Pred, pyrido, IVIg, thymectomy; Improvement

Table 1: Clinical characteristics of the UK FSHD and MG cohort. Aza – azathioprine; IVIg – intravenous immunoglobulin; MMF – mycophenolate mofetil; NK – not known; pred – prednisolone; pyrido – pyridostigmine, ritux - rituximab. Cases in italics represent non-prevalent cases.

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Ethical standards: All procedures performed were in accordance with the ethical standards of the institutional and national research committee. This work was approved by London Bridge Research Ethics Committee, REC reference 21/LO/0572.

Competing Interests: The authors declare that they have no conflict of interest.