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LETTER TO THE EDITOR

A case of facioscapulohumeral muscular dystrophy and myasthenia gravis with positivity of anti-Ach receptor antibody: a fortuitous association?

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Facioscapulohumeral dystrophy (FSHD) is the third most common form of muscular dystrophy (MD), after Duchenne muscular dystrophy and myotonic dystrophy, with a prevalence of approximately 1: 8.000–1:22.000 [1]. It is inherited mostly as an autosomal dominant disease; however, up to 30% of cases are sporadic, arising from de novo mutations. FSHD symptoms typically develop in the second decade of life but can begin at any age from infancy to late adulthood [2]. It presents clinically with asymmetric and slowly progressive weakness affecting the face, shoulder, and arms, followed by weakness of the distal lower extremities and pelvic girdle; typically, bulbar, extraocular, and respiratory muscles tend to be spared [3].

With an annual incidence of 8 to 10 cases per 1 million persons and a prevalence of 150 to 250 cases per 1 million, myasthenia gravis (MG) and its various subgroups are the major diseases that affect the neuromuscular junction. MG is an autoimmune disease in which antibodies bind to acetylcholine receptors or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction. The antibodies induce fluctuating weakness of skeletal muscle, which can be generalized or localized, is more proximal than distal, and nearly always includes eye muscles, with diplopia and ptosis [4].

Concomitant occurrence of FSHD and MG is not frequent according to the medical literature; the rare reports described previously present cases of FSHD in which MG suddenly develops and an elevated level of anti-acetylcholine receptor (AchR) antibody is detected [5, 6].

Here, we describe a patient who was a known case of FSHD with a subacute history of bulbar symptoms who was found to have MG. Patient gave her informed consent to processing personal data.

A 69-year-old woman had been clinically diagnosed with FSHD 13 years ago, confirmed by deletion analysis; family history was positive for FSHD as two brothers and one nephew were affected. Patient also suffered from hypertension and arthritis; for the arthritis, she took corticosteroids. She presented to our department with complaint of 20-day history of nasal timbre followed by dysphagia, diffuse weakness of all limbs with need of bilateral support during ambulation, and, in the last 10 days, appearance of binocular diplopia on vertical plane. Neurological examination showed winging of the scapula on the right side, wasting of proximal muscles of all limbs, anserine gait possible with bilateral support, facial and limb-girdle muscle weakness, unilateral ptosis on the left, diplopia, dysphagia, dysarthria, and depressed reflex. Serum creatine kinase values were high (414 UI/l), but other routine hematological and biochemical studies were normal. Concentric needle electromyography showed findings suggestive of myopathy. Repetitive nerve stimulation (RNS) produced a decremental response (− 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 suggestive of myasthenia gravis. Single-fiber electromyography (SFEMG) was positive with moderately increased jitter in the extensor digitorum communis (in 65%

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of 20 pairs, mean value 55.8 us, Fig. 1a, b). 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, Fig. 1b). Serum anti-acetylcholine receptor (AchR) antibody level was marked elevated (16.01 nmol/l, positive > 0.45), confirming the diagnosis of myasthenia gravis. Computerized tomography of the thorax was normal. During hospital stay, the patient was exposed to intravenous immunoglobulin therapy at 0.4 g/kg/day for 5 days and started on pyridostigmine with remarkable improvement both on clinical than on electrophysiological aspects. Neurological examination repeated after intravenous immunoglobulin documented disappearance of the ptosis; improvement of diplopia, dysphagia, and dysarthria; and recovery of lower limb strength with autonomous gait for short distances. SFEMG showed reduced pathological jitter in the extensor digitorum communis in 40% of 20 pairs with mean value of 41.4 us. After discharge, the patient was regularly visited in our clinic, and the last follow-up visit, at a distance of 1 year, showed a substantial stability both clinically and electrophysiologically.

Both FSHD and MG are rare diseases; a fortuitous association therefore seems to be unlikely. Bulbar muscle involvement and subacute onset instead of slowly progressive in a patient with FSHD is rare, so should give rise to the suspicion of another diagnosis.

Our patient presented an elevated AchR antibody level and decremental response to RNS confirming the diagnosis of MG and she started intravenous immunoglobulin therapy with dramatically improvement of the clinical signs.

The mechanism leading to MG in patients with FSHD is not well understood. AChR-abs have been reported in patients with a variety of diseases in addition to MG such as mitochondrial myopathy and limb-girdle and myotonic dystrophies [7]. The presence of AChR-abs reflects the breaking of immune tolerance to these receptors as a consequence of

Spontaneous Activity	Muscle						
	B FDI	B EDC	B BB	B VM	R MG	L MG	B TA
Fib	0/10	0/10	0/10	0/10	0/10	**3/10**	**2/10**
PSW	0/10	0/10	0/10	0/10	0/10	**3/10**	0/10
Recruit	N	N	**Early**	N	N	N	N

Quantitative analysis of Motor Unit Potential (20 MUP)					
	Mean Amp		Mean Dur		%Poly
	uV	Ref.Dev	ms	Ref.Dev	
RT Biceps Brachii	340	1.27	**10.6**	0.61	0
LT Vastus Medialis	370		12.4		4.2

Single Fiber Electromyography (SFEMG)					
LT Extensor Dig Communis	#Reg	%Increased	%Normal	Median Jitter[µs]	FD
	20	**65**	35	**55.8**	

FDI= First Dorsal Interosseous; EDC= Extensor Digitorum Communis; BB= Biceps Brachii; VM= Vastus Medialis; MG= Gastrocnemius-Medial Head; TA= Tibialis Anterior; R= Right; L= Left; B= Bilateral; Fib= Fibrillation; PSW= Positive Sharp Waves; Recruit= Recruitment; N= Normal; Amp= Amplitude; Dur= Duration; Poly= Polyphasia.

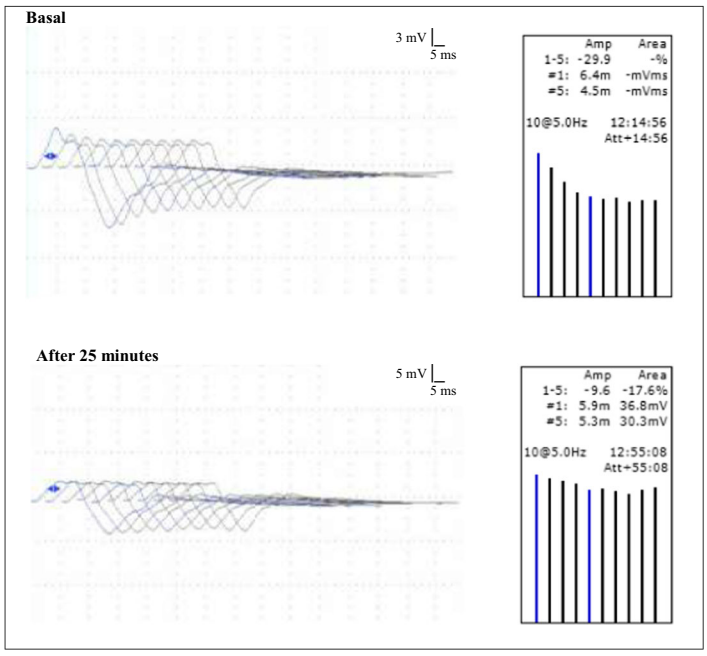

Fig. 1 **a** Basal electromyography. **b** Neostigmine test (RNS registered on left trapezius). Returning of RNS to normal after 25 min from neostigmine injection

autoinflammation secondary to muscle fiber degeneration. Small changes in the AChR structure in skeletal muscle as a result of degenerative processes might induce sensitization; this in combination with DNA or RNA particles released from degenerating tissue could engage Toll-like receptors (TLRs), which mediate inflammatory stimuli provoked by pathogens and endogenous "danger signals"; these modified antigens could then prime CD4 cells and B cells, and if sufficient, antigenic change was detected, tolerance would be broken, and autoantibody production would ensue [7].

AChR-abs are therefore interpretable as a manifestation of an immunopathic component of the muscle disease that not necessarily are associated with clear signs of MG and that explain the response to pyridostigmine and immunosuppressive therapy [7]; in our case, however, autoantibodies are responsible for the typical semiology of MG as in the other reports described in the literature [5–7].

Another aspect as support of an immune process in FSHD is the evidence that up to 80% of muscle biopsies from patients show some degree of mononuclear inflammatory cell infiltration, even if the presence of this infiltration does not affect disease progression and the patients do not benefit from prednisone treatment [6].

Concurrence of MG and FSHD therefore suggesting the possibility that immune mechanisms may be operative in FSHD; muscular degeneration acts as a "trigger" for production of AChR-abs and may manifest in MG, especially in subjects predisposed to autoimmune diseases, as this patient, who suffered also from arthritis.

In conclusion, there are limited reports of concomitant occurrence of FSHD and MG in the literature, but this association must be considered, to avoid a dangerous diagnostic delay, when any unusual changes in the course of disease or development of unusual symptoms appear, as this case shows.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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