Two cases of de novo mutation for facioscapulohumeral dystrophy in a family with myotonic dystrophy type II

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Introduction and objectives

Myotonic dystrophy type 2 (MD2) is an autosomal dominant neuromuscolar disease caused by an unstable CCTG expansion in intron 1 of gene ZNF9 on chromosome 3q 21.3.[1] Facioscapulohumeral dystrophy (FSHD) is also an autosomal dominant neuromuscolar disease associated with loss of part of a repeated sequence in the D4Z4 region on chromosome 4q35.[2] The prevalence of FSHD is 4-12/100,000 in the general population but there are not definite data about prevalence of MD2. We describe the first two cases of association of the two dystrophies, in a couple father-son, because of a de novo mutation for FSHD in a family with MD2.

Case report

A total of 11 family members in 4 generations were affected by MD2, with 2 patients, a 57-year-old male (proband) and his 29-year-old son, affected by MD2 associated with FSHD. *(Fig. 1)* Disease onset was at 40 years in the proband, with difficulty in arising from chair and bed, and at 13 in his son, with impaired bilateral arm elevation. The two patients display now a diffuse muscular involvement, reminiscent of both disorders: facial hypomimia, severe proximal limbs muscles pain, axial and proximal limbs muscle weakness *(Fig. 2-3)* and hypotrophy with calf hypertrophy as well as a bilateral winged scapula associated with lumbar lordosis. Distal limb muscles are proportionally spared. The proband is also affected by diabetes mellitus and effort dyspnoea, with decrease in clinostatic FVC. At present, proband needs braces or walker for walking, his son is still able to walk with severe hyperlordosis. Muscular dystrophy phenotype is more severe in proband and his son in comparison with the other members of the family.

Methods and results

An extensive muscle electromyographic assessment (EMG) including neck, shoulder, abdominal, pelvic and lower limb muscles document EMG features typical of DM2 and FSHD: short-amplitude and short-duration MUAPs with abnormal pattern at maximal volitional effort. Myotonic phenomenon has not been evidenced. A biopsy of the vastus lateralis muscle was also performed on the proband and showed hystopathologic features of muscular dystrophy. Molecular genetic studies confirmed the presence, in both the proband and his son, of the two neuromuscolar diseases: short-range PCR, XL PCR and Southern Blot revealed a pathologically expanded ZNF9 allele with high molecular weight on chromosome 3 (compatible with MD2) and Southern Blot hybridization found a contraction in the 3.3 Kb D4Z4 tandem repeat at 4q35 compatible with FSHD. Myotonic dystrophy 2 mutation was confirmed in all available affected family members.

Discussion and conclusions

This is the first description of the coexistence of MD2 and FSHD in the same patients. Considering the prevalence of these muscular dystrophies (MD2 in particular), the chance of a “double-trouble condition” related to these genetic disorders must be considered very rare. As observed in a previously reported case of the coexistence of the more common myotonic dystrophy type I and FSHD, the concurrence of two distinct muscular dystrophies in the same patient leads to development of a more severe muscular phenotype.[3] In families with muscular dystrophies, members with an atypical presentation should perform a more extensive genetic testing.

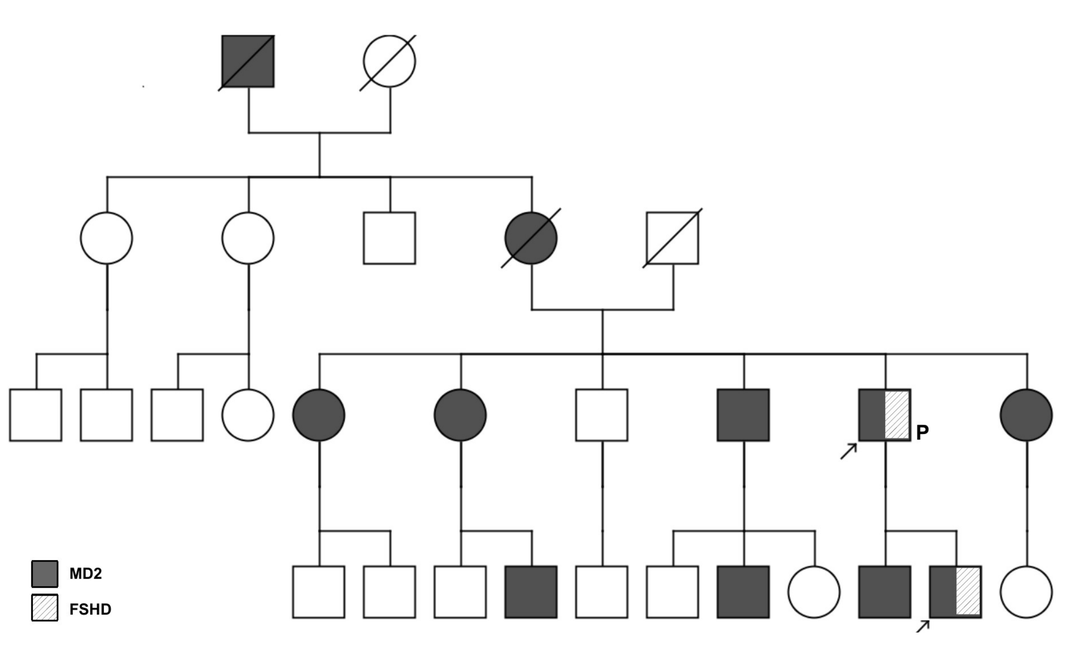

Fig.1 – Pedigree of the family.
*In an analysis of four generations, 11 members resulted affected by MD2, confirmed by DNA testing and/or high suggestive clinical features. The proband **(P)** and his son are affected by both MD2 and FSHD **(arrows)**.*

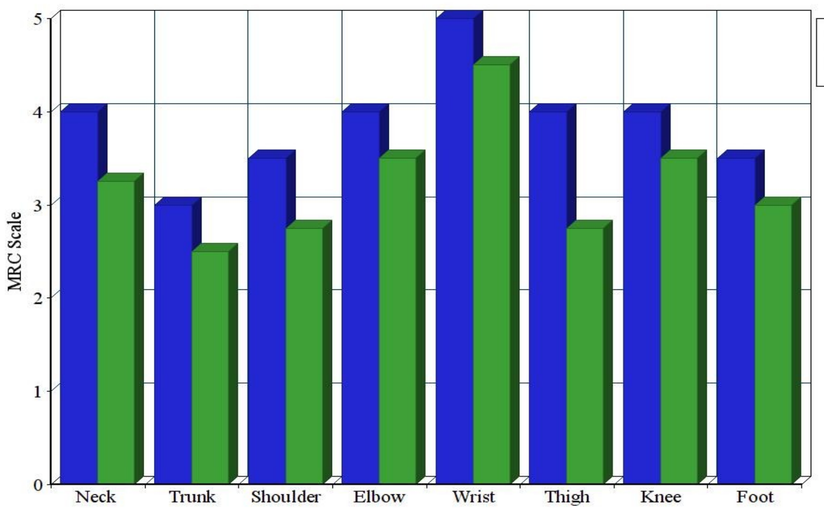

Fig.2 – Bilateral Flexor Muscles Strength in the proband.
Clinical MRC Scale evaluation showed a significant increase in weakness in flexor muscles, from 2009 to 2016. Proximal and axial groups are more affected.

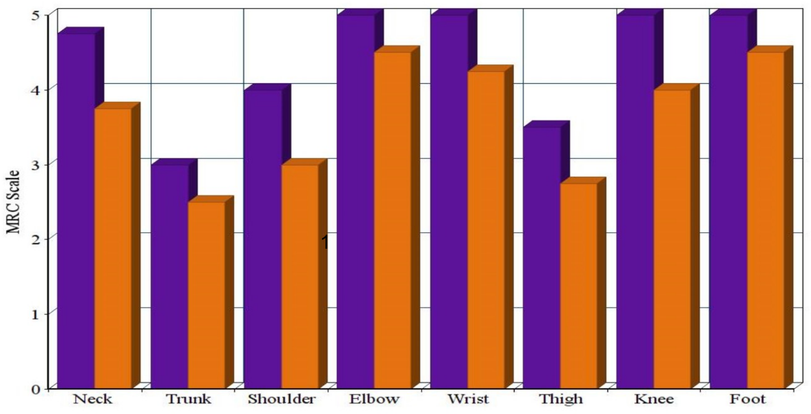

Fig.3 – Bilateral Extensor Muscles Strength in the proband.
Also for extensor muscular groups, from 2009 to 2016, clinical evaluation revealed a significant worsening of weakness, predominantly in proximal and axial muscles.

References

1.Thornton CA. *Myotonic dystrophy*. Neurol Clin. 2014 Aug;32(3):705-19.

2. Wang LH, Tawil R. *Facioscapulohumeral Dystrophy*. Curr Neurol Neurosci Rep. 2016 Jul;16(7):66.

3. Masciullo M, Iannaccone E, Bianchi ML, Santoro M, Conte G, Modoni A, Monforte M, Tasca G, Laschena F, Ricci E, Silvestri G. *Myotonic dystrophy type 1 and de novo FSHD mutation double trouble: a clinical and muscle MRI study*. Neuromuscul Disord. 2013 May;23(5):427-31.