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LETTER

Symptomatic female carriers of mutations in the Duchenne muscular dystrophy gene

Mulheres sintomáticas portadoras da mutação do gene de distrofia muscular do tipo Duchenne

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Dear Editors,

We read with interest the article published by Silva et al.[1] on functional performance and muscular strength in symptomatic female carriers of the Duchenne muscular dystrophy (DMD) gene. If a female individual carries the dystrophin gene mutation on one of the two chromosomes, the second X-chromosome 'protects' her due to the production of a regular dystrophin protein. However, some of these female carriers can present symptoms varying from mild muscle weakness to a more severe course, being classified as symptomatic carriers. Age at symptom onset in female carriers ranges from 15 to 31 years (mean of 30.6 years), and age at diagnosis for asymptomatic carriers ranges from 4 to 38 years (mean of 24.5 years)[2]. They usually present with asymmetric bilateral leg weakness and can develop myalgia, cramps, fatigue, dilated cardiomyopathy, and enlarged calf muscles (pseudohypertrophy) with elevated serum creatine kinase (CK) levels.

We had two cases of female symptomatic carriers of the dystrophin gene, mothers of two boys, both showing duplication of exons disturbing the open reading frame of the DMD gene. Both of them had significant limitation of their functionality, causing limitation in the physical support for their sons. We propose that they should be classified and treated as patients with the disease.

The first case was a 38-year-old woman with weakness in upper and lower limbs, leading to frequent falls and pain during efforts, which began by age 18. Neurological exam revealed proximal muscle atrophy in the right lower limb (flexors, extensors, and adductors of the hip graded 3/5) and interosseous muscles of both hands. Serum CK levels were elevated at 1,500 U/L (normal values range from 26 to 192 U/L), and electromyography (EMG) studies showed myopathic changes. Cardiac investigation, including echocardiogram and 24-h Holter analysis, were regular. She had a son with DMD, which prompted us to ask for molecular analysis of the dystrophin gene that revealed a pathogenic duplication of exons 8 and 9 modifying the open reading frame of the DMD gene by means of the Multiplex Ligation-dependent Probe Amplification (MLPA) method.

The second case is a 32-year-old woman whose son was diagnosed with DMD. She became symptomatic 10 years before, presenting with gait difficulties and frequent falls. She developed myopathic gait, lumbar scoliosis, and needed unilateral support. Neurological exam revealed muscle strength 3/5 proximally in the lower and upper limbs, involving flexors, extensors and abductors of the shoulder and flexors, extensors, and adductors of hip muscles. CK levels were 2,366, but they ranged from 10 to 20 times the normal value (ranging from 26 to 192 U/L) throughout the years. Cardiac investigation was regular. MLPA molecular analysis of the dystrophin gene revealed duplication of exons 60 and 62 modifying the open reading frame of the DMD gene.

Development of symptoms in DMD mutation carriers has been attributed to skewed X-chromosome inactivation (XCI), in which the X chromosome expression with the DMD mutated allele is favored[3]. Juan-Mateu et al[3]. showed that the extent of XCI skewing is related to phenotype severity, with symptomatic carriers exhibiting 49.2% more skewed XCI profiles than asymptomatic carriers. However, this mechanism is still controversial. The first study that deeply explored the DMD transcriptional behavior found no relationship between the total DMD transcript level and the relative proportion of the wild-type transcript, with the symptomatic phenotype[4].

Zhong et al.[5], in their clinical and genetic study of 78 female dystrophinopathy carriers, including four symptomatic and 74 asymptomatic carriers, found that all symptomatic carriers had a duplication mutation. Among asymptomatic carriers, almost 42% had deletion mutations, while around 45% had point mutations in exons and only 13.5% cases carried duplication mutation. MLPA for the dystrophin gene exons,

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along with next-generation sequencing and Sanger sequencing, were effective for diagnosing symptomatic carriers and determining the status of probable carriers. The authors also showed that CK levels have high diagnostic sensitivity and specificity among female carriers. In our two patients, we found duplication mutations by means of the MLPA method. Silva et al.[1] found only one duplication, with deletions being the most common mutation in seven patients.

We have presented herein two illustrative cases of female symptomatic 'carriers' with significant motor impairments. Our major limitation was the lack of additional tests (in particular, muscle magnetic resonance imaging and biopsy) to ascertain that no additional cause was responsible for myopathic symptoms or to provide pathogenicity evidence in the investigation of atypical DMD presentations. Even though muscle biopsy was not performed, clinical and laboratory tests excluded other potential causes for myopathy, such as immune-mediated or toxic ones. By definition, the word 'carriers' is applied to someone with unexpressed genetic trait without disease symptoms. We therefore propose that female symptomatic patients should no longer be classified as carriers and should be appropriately evaluated and treated. Since we still have no guidelines or expert recommendations, the treatment of our two patients was not pursued. However, we stress the need to further discuss treatment in these patients, mainly through steroids.

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