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Case report

Phenotypic contrasts of Duchenne Muscular Dystrophy in women: Two case reports

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ABSTRACT

We discussed two cases of symptomatic female carriers to Duchenne Muscular Dystrophy. The first case is a 20 year-old girl with classical phenotypic manifestation of the disease, similar to the condition in boys. The case 2 is a 62 year-old woman with progressive muscular weakness. The disease is much less common in woman than men so both cases described here are considered rare forms of the disease, with several clinical implications. In both cases, a progressive muscle weakness, impairment in walking and sleeping was observed, in addition to obstructive sleep apnea syndrome and alveolar hypoventilation, that required noninvasive ventilatory support.

1. Introduction

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive neuromuscular disease. This fatal disease affects approximately 1:3,500 to 6,000 live male births [1] and 1:50,000,000 live female births [2,3]. It is a neuromuscular disorder characterized by a mutation in the dystrophin (*DMD*) gene caused by deletions (65% of cases) [4], specific mutations (26% of cases) [5], duplications (7% of cases) [6] and other unidentified causes (about 2% of cases) [5].

In general, women with an abnormal X chromosome are asymptomatic as long as it is compensated by the other normal allele. Cases of DMD in which the patient develops a similar phenotype as the male gender are rare in women [7]. Women may be symptomatic carriers of DMD when they are affected by homozygous mutations in the dystrophin gene, with partial or total expression of the abnormal gene. The signs and symptoms in women can vary from mild muscular weakness to severe clinical complications, when the patient is defined as a manifesting or symptomatic carrier. About 20% of heterozygous female carriers have the characteristic signs of the disease [8]. Often, carriers are symptomatic due to chromosomal translocations, Turner syndrome [9,10] or abnormal X chromosome [11]. Women have two X chromosomes and are normally not affected by X-linked disorders, due to the capacity of the unaffected chromosome to compensate for the deficiency of the abnormal gene of the other chromosome. A number of females with X-autosome translocations with breakpoint in the Xp21 locus have also been shown to manifest signs and symptoms of DMD. One interpretation is that the gene locus is in that region, and that the locus on the normal X is inactivated, a mechanism called preferential inactivation of the X. On rare occasions, an X chromosome may be completely missing or present with a particular breaking point disrupting the dystrophin gene [12].

In women, the muscle weakness is usually mild, with asymmetric predominance and proximal distribution [13]. The onset of symptoms in affected women is variable. It can be observed from the first until the fourth decade of life. It is noteworthy that those who manifest before 15 years-old often have greater impairment and severity of clinical manifestations [13,14]. In this study we described two case reports of female carriers of DMD, representing manifestations in a young and an adult women.

2. Case report

2.1. Case 1

Female, single, 20 years-old, born preterm but otherwise a normal pregnancy without complications. Parents are not consanguineous and the first case of DMD in her family. Within 18 months showed hypertrophy of the calf. At five years-old, the child begun to show difficulties in getting up from the sitting position

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Table 1
Polysomnography findings in symptomatic female carriers of Duchenne Muscular Dystrophy.

	Case 1 (PSG 1)	Case 2 (PSG 1)	Case 2 (PSG 2)
Total sleep time (min)	423.5	324.4	233.0
Sleep efficiency (%)	84.2	80.0	55.3
Sleep latency (min)	14.0	20.2	45.4
REM sleep latency (min)	81.5	351.5	–
Wake after sleep onset (min)	63.5	61.0	143.0
Arousal index (events/hour)	3.3	15.2	24.2
Stage 1 (%)	2.8	5.4	26.2
Stage 2 (%)	39.2	69.0	64.8
Stage 3 (%)	33.2	16.3	9.0
Sleep REM (%)	24.8	9.2	0
Obstructive apneas index (events/hour)	0	0.6	2.3
Central apnea index (events/hour)	0	0	0
Mixed apnea index (events/hour)	0	0	0
AHI (events/hour)	0.3	5.7	13.4
SpO_2 < 90% (min.)	4.0	1.5	26.2
Desaturation events < 3% (n)	6.3	40	57

Legend: REM = rapid eye movement; AHI = apnea hypopnea index; SpO_2 = oxygen saturation. Polysomnography was performed without use ventilation in all cases. In Case 1 patient with age at 10 years old and in Case 2 patient in PSG 1 with age at 61 years old and in PSG 2 with age at 62 years old.

(Gowers' sign) and constant falls. The disease had a rapid clinical course with progressive weakness in the lower limbs and foot deformities. At nine years-old, she lost the ability to walk and began to use a wheelchair and consequently became progressively obese. Menarche was at ten years-old. At 10 years old, she presented complaints of dyspnea on moderate efforts, diurnal headache, snoring, nocturnal sweating and witnesses apnea during sleep. She has a complete diagnostic polysomnography (PSG) that showed preserved sleep architecture and sleep efficiency (Table 1), although mild snoring, rare hypopneas events and 0.2% of total sleep time with SpO_2 below 90% was detected. Spirometry showed 64% of forced vital capacity-FVC (1.35 L) and FVC/forced expiratory volume (FEV1) = 101. At 11 years old patient persists with headache and dyspnea. The patient had gain 10 kg of body weight. FVC = 0.85 L (31%), FEV1 = 0.83 (33%), FVC/FEV1 = 98. At that moment, NIV therapy was started due to the low forced vital capacity and symptoms. She had good adherence to the noninvasive ventilation (NIV) device using it for about 6 h/night. At 11 years-old, she was with 61 kg and 1.58 m. Three years later, she presented a considerable weight gain, being 78.1 kg and 1.65 m, without corticoid use. At 17 years-old, she was diagnosed with dysphagia, and consequently suffered a significant weight loss (42.5 kg and 1.65 m). One year later this had progressed to anorexia (35 kg and 1.65 m) and underwent gastrostomy. Currently, the patient is confined to bed and receives mixed feeding (oral and gastrostomy). She has motor strength grade 1 in four members and fibrous tendon retractions and uses noninvasive mechanical ventilation with bi-level positive airway pressure parameters in spontaneous/timed mode with a respiratory rate of 12 per min, inspiratory pressure of 16 cm H_2O, expiratory pressure of 4 cm H_2O, generating tidal volumes of 200–400 mL.

The karyotype was performed by G-banding with analysis of metaphases from temporary lymphocyte cultures of peripheral blood. Result revealed karyotype 46,X,t(X;4)(p21;q13) [20], with a reciprocal translocation involving the short arm of the X chromosome and the long arm of one chromosome 4, with breakpoints in Xp21 and 4q13. In addition, microarray analysis of chromosomal aberrations and copy number variants was performed. In this case, the test did not show copy number variations within *DMD* gene; however, a 471 kb duplication in the pseudoautossomal region PAR1 (arr[hg19] Xp22.33(524,439 – 995,018) × 3) was found, overlapping the *SHOX* gene (OMIM #312865).

2.2. Case 2

Women, married, 62 years-old, who reported onset of weakness of the muscles of the lower limbs at 56 years of age, with progressive evolution year-by-year. Had 2 pregnancies, 1 son with DMD, who died with aged 19 years-old, and a healthy 35 year old daughter. Also complained of snoring, apneas, daytime sleepiness, mood changes, morning headache, sudden awakening and fragmented sleep. At that time, she was taking sertraline (50 mg), amitriptyline (25 mg), diazepam (10 mg) and metformin (500 mg). At 61 years old, spirometry showed 83% of FVC (2.41 L) and FVC/FEV1 = 107. The PSG report showed a mild increase of the respiratory disturbance index due to obstructive events, increased N2 stage (64.8%), reduced sleep efficiency (80%) and REM sleep (9.2%), mild snoring and oxygen desaturation. The oxygen desaturation index was more pronounced in REM sleep. End-tidal carbon dioxide remained 166.9 min (51.4%) of total sleep time above 50 mmHg. For this reason, mechanical ventilation was indicated with bi-level positive pressure. She had good adherence to the treatment and reported important improvement in the previous symptoms. At 62 years old, the patient was submitted to a new PSG to monitoring since the first polysomnography was performed at baseline (without NIV). A new baseline polysomnography was performed to verify whether the patient´s subtle symptoms reflect abnormal nocturnal gas exchange, showing a slight increase in apnea-hypopnea index (13.4) due obstructive events, and increased respiratory disturbance index (22.1 events/hour) mainly caused by respiratory effort related to arousal; mild to severe snoring; sleep efficiency reduced to 55.3% as a result of increased sleep latency and frequent awakenings; reduction in slow wave sleep and absence of REM sleep; increase in arousal index (24.2 events/hour). She presented 26.2 min of oxygen saturation below 90% (8.1% of total sleep time). Currently, she has a myopathic gait and walks with the aid of a walking stick. Her muscular weakness is proximal grade 4 and distal grade 5 in her right arm, as well as proximal grade 3 and distal grade 5 in her left lower limb. She reported the onset of severe pain in the lumbar region, related to body posture. After a few months, she complained of frequent falls while walking. The patient evolved with the onset of progressive weakness in the lower limbs initially and subsequently in the upper limbs. She reported “a trembling sensation in the body” and chronic widespread pain. She presented other co-morbidities such as diabetes mellitus, chronic constipation and depressive disorder.

The additional examination of karyotype by G-banding of peripheral blood revealed a normal karyotype 46, XX with a resolution level of 440–550 chromosomal bands. However, through the microarray analysis of chromosomal aberrations and copy number variants, a duplication of exons 43–52 of the dystrophin gene was identified, being classifiable as a manifesting carrier. The microarray test revealed two pathogenic gains in these patient, within the *DMD* gene (arr[hg19] Xp21.1(31,746,944 – 31,923,772) × 3 and arr[hg19] Xp21.1(32,110,375 – 32,328,188) × 3, with 177 kb and 218 kb respectively. These variants overlap exons 42–44 and 48–52 of *DMD* gene (OMIM #300377), respectively.

3. Discussion

The patients described in this report represent uncommon clinical manifestations in women with DMD. Case 1 is of a 20 year old with clinical features of DMD (early symptoms since 18 months of age). She has muscular weakness, loss of gait and is underweight. Low weight is due to severe muscle atrophy and the

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