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## Case Report

# Restless leg syndrome exacerbated by amitriptyline in a patient with Duchenne Muscular Dystrophy



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## ABSTRACT

We report an unusual case of a Duchenne Muscular Dystrophy(DMD) patient who initiated a restless leg syndrome after the use of amitriptyline. The prescription and use of this medication for patients with persistent neuropathic pain is relatively common, especially for patients with DMD. Normally, this medication is well tolerated, however, we now report the occurrence of an induction or intensification of a restless leg syndrome case in a young patient with DMD, treated with amitriptyline for his chronic pain.

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## 1. Introduction

Duchenne Muscular Dystrophy (DMD) is a neuromuscular disease linked to the X chromosome which afflicts 1 in every 3500 born boys. DMD is caused by a mutation on the dystrophin gene at locus Xp.21, leading to dystrophin absence or a production defect in the muscles. Affected individuals demonstrate progressive loss of muscle tone and respiratory, cardiac and orthopedic impairment. Loss of walking capacity usually occurs around 9–11 years of age and death between 20 and 30 years of age [1]. Neuromuscular diseases, in general, may be developed by chronic pain as a result of contractures, deformities and immobility, with great impact on the quality of life

[2]. Pharmacological treatment with amitriptyline chloride constitutes one of the multimodal aspects of intervention for the pain treatment in patients with neuromuscular diseases [3]. There is a possible association between tricyclic antidepressants and the restless leg syndrome (RLS) [4].

We presently report a case where a patient with diagnostic of DMD demonstrated a marked worsening of his RLS, associated with the use of amitriptyline.

## 2. Case report

Male patient with 27 years of age, with diagnostic of Duchenne Muscular Dystrophy at the age of 7 years. Beginning of

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**Table 1 – Probability scale of DAR of Naranjo et al. [11].**

Criteria for the definition of causal relationship	Yes	No	Undetermined
Are there conclusive reports about this reaction?		0	
Has the clinical event appeared after the administration of the suspected drug?	+2		
Has the reaction disappeared when the suspected drug was discontinued or when the specific antagonist was administered?	+1		
Has the reaction reappeared when the drug was reinstated?			0
Are there alternative causes (other than the drug) which could provoke that reaction?		+2	
Has the reaction reappeared when a placebo is given?			0
Has the drug been detected in the bloodstream or in other biological fluids in well known toxic concentrations?			0
Does the reaction increases with the increase of the drug dosage or becomes less severe with drug reduction?	+1		
Does the patient have a history of similar reaction to the same drug or a similar one in some previous exposure?			0

symptoms at the age of 6, with myopathic walk and difficulty in climbing stairs. Loss of walking ability at 10. With 19 years old, evolved to alveolar hypoventilation syndrome and the need of ventilatory support with non-invasive mechanical ventilation. At this age, the patient already demonstrated movement restriction, with global tetraparesis. At the age of 23, initiated with diffuse and continuous chronic pain, worsening of passive limb movements and daily chronic migraine resulted from analgesic abuse. We then initiated treatment with a tricyclic antidepressant (amitriptyline chloride 25 mg/night). After a few days of therapy the patient referred a feeling of undetermined discomfort in his inferior limbs, beginning every day in the evening, with intense will to move his legs, only relieved by passive movement of his legs (done by his caretaker since he was incapable of doing it himself). The phenomenon lasted for 2 h, making it difficult to sleep and with spontaneous remission. The patient had demonstrated similar symptoms previously although with less intensity, duration and frequency. There was no evidence of periodic limb movements (patient with global tetraparesis and motor strength grade 1, making it impossible to move the limbs), peripheral neuropathy, spinal radiculopathy or other associated conditions. He had positive familiar history (mother refers some characteristically similar episodes, not related to any drug usage, with low frequency and intensity). Blood tests were considered normal. With the interruption of the medication, after approximately 30 days, the patient showed marked improvement of this condition, with decrease of the episodes and symptoms, maintaining its eventual frequency. The punctuation of the Naranjo and cols Drug Adverse Reaction (DAR) probability scale (1981) was of 6 points, indicating a probable side effect of the drug (Table 1).

### 3. Discussion

Patients with DMD show high risk for the development of respiratory disorders related with sleep, mainly the sleep obstructive apnea syndrome and alveolar hypoventilation [5]. Other sleep disorders include difficulty in initiating and maintaining sleep. Many patients show important sleep fragmentation with frequent awakenings for decubital

changes (by the caretakers) due to pain or discomfort [6]. There is very little information about movement disturbances during sleep in these patients.

RLS is a motor-sensitive disorder related to sleep, characterized by discomforting or painful paresthetic sensations in the legs, between the ankle and the knee at rest, accompanied by the intense need to move the affected limbs. The RLS physiopathology is still not established; however, there are some hypothesis related to the mechanisms of central and peripheral nervous system processing and some elements of the motor system, as well as the dopaminergic and iron metabolisms systems. RLS may be classified as idiopathic, genetic with a dominant autosomic heritage pattern, or secondary to a subjacent clinical condition. The RLS diagnosis is exclusively clinical, obeying the minimal criteria in accordance to the International Restless Legs Syndrome Study Group – IRLSSG and of the International Sleep Disorders Classification of 2005, being essential criteria the following: irresistible and intense need to move the legs, generally accompanied by discomfort or inconvenience; the symptoms worsen or are exclusively present at rest or during inactivity, sitting or laying down; the symptoms are alleviated totally or partially with movement; symptoms worsen or occur exclusively at night. The described symptoms are not best explained by any other diseases of conditions. The support criteria for diagnostic of RLS are: elevated index of periodic leg movement during sleep; positive familiar history; therapeutic response to dopaminergic agents; clinical course [7,8].

Several medications do appear to possess the potential to induce or intensify RLS, including antiemetics, antipsychotics and antidepressants (tricyclic, serotonin reuptake inhibitors, selective noradrenergic-serotonergic) [9]. Amitriptyline chloride is a potent antidepressant with sedative and anticholinergic properties, acting by inhibiting the membrane pump mechanism responsible for the norepinephrine and serotonin uptake by adrenergic and serotonergic neurons. It also shows, in less proportion, activity upon the blockage of dopamine reuptake, with possible psychomotor activation [12], this action being possibly related to the development of RLS. It is considered one of the drugs of first choice for the treatment of chronic pain, acting upon different nociceptive mechanisms. Some of its side effects include excessive

sleepiness, insomnia, nightmares, paresthesias and extrapiramid symptoms [3]. These effects might result in sleep disturbances.

Establishing a relationship cause/effect between a clinical event and the use of a medication presents intrinsic difficulties, bearing in mind inespecificity and the superimposition of several factors. One way of establishing a causal relationship with higher security is the use of algorithms with diagnostic criteria for DAR, such as the probability scale of DAR according to Naranjo et al. [11]. In this system, a punctuation between 5 and 8 indicates a probable causality, establishing that the reaction follows a reasonable chronological sequence from the initial administration of the drug, with a previously know response and which cannot be totally explained by the clinical course of the patient [10,11].

The patient here described demonstrated 4 of the 5 essential criteria for RLS and positive familiar history, associated with a relatively high probability of causality with a drug side effect. The criterion related to the beginning of the symptoms at rest or during inactivity periods, could not be evaluated or observed, due to the patient's global tetraparesis condition, making him totally restricted to bed during day and night timeframes. Considering the relaxation concept and incorporating the level of activity of the central nervous system with the decrease of the vigil level, then we determined that the patient really demonstrated all the essential criteria, once the symptoms only arose when the patient was beginning to sleep. This case describes a probable and rare side effect of amtryptiline related to sleep in a patient with DMD.

#### 4. Conclusion

We point out the importance of this association and identification due to its great discomfort described by the patient. This clinical symptom is of major importance since the patient with DMD is incapacitated of own motor mobility as a way to relieve his condition, therefore leading to a physical and emotional distress. In our knowledge, this is the first description of such association between tricyclic antidepressant and RLS in DMD. We point out that the association of medication with RLS is described in small series and case reports and the presently here described association must be interpreted with caution and be confirmed in other more structured studies in the future.

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