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Clinical Case

Clinical Case Description of a Restless Legs Syndrome and Coenzyme Q10 Therapy

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Abstract

The present study is a clinical case description of a patient with diabetes without neurophysiological signs of metabolic neuropathy, with low serum iron levels, in treatment with a statin, who presented a classic Restless Legs Syndrome, with particular evidence of cramp-like symptoms. Laboratory tests and clinical examination showed no signs of peripheral muscle or neurogenic damage. However, the patient benefited from the use of high-concentration coenzyme Q10 therapy also on RLS, which was fully resolved by the association with the classical dopaminergic therapy; the case observation showed a possible important role of coenzyme Q10 antioxidant in the therapy of RLS.

Keywords: RLS; diabetic neuropathy; sideropenia; muscle statin damage; coenzyme Q10; antioxidant therapy

Introduction

Restless Legs Syndrome (RLS) is a disease well known by neurologists, characterized by the uncontrollable urge to move the legs, often associated with a sensation of discomfort, pain or tingling in the lower limbs, while lying down, mainly in bed during night-time, but in some cases also otherwise resting. It is a disabling disease as it compromises sleep-wake rhythms and is often associated with anxiety and depression. Several causes of the disease are listed, such as peripheral neuropathies, like mostly diabetic neuropathy, arthrosis and discopathies of the lumbosacral spine with compressive damage of the emerging nerve roots, namely lumbosacral stenosis. In many cases it is possible to detect a comorbidity with lung pathologies that interfere with the quality of sleep, such as obstructive sleep apnea syndrome (OSAS). In other cases the patients are affected by sideropenia. Moreover, it is not uncommon to record a family history with other movement disorders, such as Parkinson's disease (PD), Essential Tremor (ET), dystonic syndromes, or even the coexistence with some of these pathologies in the same patient [1-9] However, in many cases it is not possible to establish a comorbidity or a genetic impact to which attribute the aetiology and pathogenesis, but the disorder is idiopathic. The main therapeutic tools known and used for pharmacological treatment are dopamine agonists. The therapeutic and preventive role of antioxidant molecules in neurodegenerative diseases and movement disorders has been argued in some studies and in clinical practice; in any case antioxidants (AO) are used anecdotally and empirically by specialists and physicians who are confident in their effectiveness, although not finding reference in guidelines [10-13]; many physicians do not consider their usefulness reliable instead. This study presents a clinical case of a patient with RLS in whom the antioxydant coenzyme Q10 had an interesting and noticeable role in the complex of therapeutic interventions.

Clinical case description

The case under description concerns a man 75-year-old at the time of the first clinical examination in the Movement Disorders Clinic, who was retired after having worked as a lift operator for many years. In the family history there were two deceased siblings, a brother and a sister, affected by "dementia", without a more specific definition. He had been a smoker in his youth and did not report alcohol consumption. He uderwent to an L5-S1 discectomy about 30 years previously and 25 years earlier to a repair operation for a lesion of the right scapular-humeral joint. Moreover, in the remote history he reported prostatectomy and mini-invasive knee bilateral unicompartmental arthroplasty. He also suffered from vertigo syndrome, treated by an ENT specialist and diabetes treated with oral therapy. In 2021, on the advice of his general practitioner, he had undergone a brain Magnetic Resonance Imaging (MR) which had shown signs of brain vasculopathy with leukoaraiosis classified as grade 1 according to Fazekas score. The patient came to the outpatiens' clinic for Movement Disorders complaining of a slight impairment in short-term memory and discomfort in the legs consisting of an indefinable pain and cramps as well as annoying tingling sensation that initially appeared only when lying in bed at night, lately the symptoms appeared also while resting on the couch during the day. These

discomforts forced him to move his limbs or assume a sitting position to rest the soles of his feet on the floor in an attempt to find relief. He did not report snoring or difficulty breathing while sleeping. For that reason he was sent by the general physician to the neurologist. At the first clinical examination the patient complained the appearance of the symptoms in the last two years, with a prominence of cramps, which occurred as soon as he lay in bed at night as a start of a growing discomfort and the subsequent urgent need to move the legs, and causing insomnia. No family history of movement disorder diseases RLS-like or others was reported. The neurological objective examination was normal: tone and trophism were physiological, osteotendinous reflexes (OTR) were normal or hypoevoked, district muscle strength was preserved; no tenderness was detected on muscle palpation while resting or on effort; superficial and deep sensitivities unscathed, the cranial nerves and the facies were normal. Furthermore, no signs of venous phlebopathy or stasis, skin dystrophies, or superficial ischemic signs were evident on objective examination. The patient did not report pain in the lower limbs during walking. He was on antiplatelet therapy with acetylsalicylic acid and, important detail, a statin to reduce cholesterol's levels; moreover, due to diabetes he assumed oral hypoglycemics and subcutaneous hypoglycemic therapy (dulaglutide), and antihypertensive drugs. The following tests were requested: serum iron and ferritin levels, serum creatine phosphokinase (CPK) level, blood electrolyte dosage, electromyographic examination, pneumological consultation for polysomnographic study if necessary.

Test results and therapy

Considering that the symptoms reported by the patient were consistent with the clinical diagnosis of RLS, maybe associated to diabetic neuropathy, in order to try to bring rapid relief to the disorder, a therapy based on antioxidants known for their efficacy in diabetes, particularly in diabetic neuropathy, was immediately started. Therefore, an attempt was tried with coenzyme Q10 (the highest daily dosage of 200 mg), commercially available in association with doses of L-carnitine, folic acid, vitamins B6 and B12. The commercial formulation adopted contained the highest dosage in coenzyme Q10 (coQ10) supplements, which is also found in many supplement products used for various therapeutic indications. In a few days the patient reported a clear improvement with remission in particular of the cramp-like symptoms only with the supplement-based therapy, however less evident on the motor disorder of the lower limbs. Therefore, pramipexole therapy was subsequently added, at a dose of 0.18 mg in the evening, with further improvement and remission of the motor symptom. In the meantime, the patient underwent the required tests: Electromyography performed on the lower limbs, with conduction velocities, was within normal limits, therefore no neurophysiological signs of diabetic neuropathy were highlighted; iron and ferritin levels were reduced (respectively 37ug\dL,with normal range within 65 to175 ug and 12ng\ml, with normal range 30 to 300 ng); glycosylated hemoglobin was 7.7, total cholesterol 144 mg\dl, with LDL 63 mg\dl; CPK was 58 U\L, with normal range within 0-171. Serum electrolytes were normal. The pulmonary consultation confirmed a moderate chronic bronchopathy, without specific indication for further test polysomnography.

The patient attempted to stop taking the supplements, but had a recurrence of the cramp-like symptoms and a concomitant worsening of the RLS, even with regular intake of pramipexole. However, the use of the supplement alone was not sufficient to cover the symptoms (coercive movements of the limbs in a lying position), which seemed nevertheless to be closely linked. However, it was necessary to correct the low sideremia values with an additional iron supplement, which was introduced into the therapy despite the reluctance of the general practitioner, as the patient did not present anaemic alterations in the blood count and had low gastric tolerability. However, it is noteworthy that it resulted difficult to obtain a normalization of sideremic values in the subsequent observation period.

Discussion

As is known, Restless Legs Syndrome (RLS) is a disease characterized by the uncontrollable urge to move the legs, while lying down, mainly in bed during night-time, but in some cases also otherwise resting [13,14]. In many cases the causes remain unknown, although numerous factors and comorbidities are described in the literature and are known in clinical experience, including, in addition to those already listed, fibromyalgia and vascular and venous diseases of the lower limbs. The case described was interesting because in the clinical presentation there were different early evident data easily able to explain the disorder as concerns aetiology, such as diabetes, in particular the possible related peripheral neuropathy, but also the reduction of the iron serum levels: in fact, it is common clinical experience that the correction of sideremia alone leads in many cases to a remission or a drastic improvement of RLS, even if sometimes temporarily. However, the electromyographic examination was normal as far as the diagnostic suspicion of diabetic neuropathy and not significant for any neurophysiological signs attributable to radicular damage, although the patient underwent L5-S1 discectomy many years before. Furthermore, the patient's description gave remark to the presence of cramps, therefore it was plausible to consider a possible myotoxic effect of the statin on the symptom, even if taken at a low dose; however, the serum CPK levels were normal. Coenzyme Q10 (2,3 dimethoxy-5 methyl-6-decaprenyl benzoquinone) is a fat-soluble, vitamin-like quinone commonly known as ubiquinone, also called "vitamin" Q10, although not properly, as it is synthesized from the organism [15,16]. It is known that coQ10 counteracts the myotoxic effects of statins, therefore its effectiveness in alleviating the patient's symptoms could initially be attributed to this already known property [17-21]. Moreover, the patient's description focused heavily on the presence of cramps, therefore it was plausible to consider a possible myotoxic effect of the statin, even if taken at a low dose; however, since there were no biochemical signs of muscle damage, this explanation appears disputable. Furthermore, the patient, although making a remark in the distinction between cramps and the urge to move the limbs in a supine position, closely linked the two symptoms, as part of a single syndrome; in this regard, in RLS cramps are often present among the irritative symptoms. Moreover, this symptom could not be attributed to diabetic neuropathy, spine stenosis and\or to sleep breathing disorder. Furthermore, classical dopaminergic therapy with pramipexole was found to be effective, also confirming the diagnosis. It is also interesting the difficulty found in this patient in maintaining a long time physiological levels of sideremia. What the mechanism of action of coQ10 may be in this and other cases remains uncertain: from a biochemical point of view, it supports energy metabolism, with an influence on ATP; it has an antioxidant function, helps to increase the bioavailability of ascorbic acid and tocopherol and has a neuroprotective action. The physiological levels of coQ10 decrease with age and in pathological conditions, therefore supplementation can reverse this trend [22-25]. In previous episodic experiences of this Author, the efficacy of AO, in particular coQ10, has been found in patients with RLS particularly associated with diabetic neuropathy. For instance, in a case of a home patient with severe diabetic neuropathy and RLS, the use of supplements for diabetic neuropathy that included coQ10 allowed the remission of the symptoms related to RLS and in part of the neuropathy itself, without using any dopaminergic therapy; substitution with non-coQ10 supplements resulted in worsening and recurrence of symptoms. The effects of coQ10 on diabetic neuropathy and statin-induced muscle damage are well known and described in literature; it is also utilized in cardiological treatments. In this case, it is interesting to note that the efficacy

appears evident in a preclinical phase with respect to diagnostic and instrumental markers, like positive biochemical or neurophysiological results, and has a direct impact on the symptoms' manifestation of RLS. CoQ10 therapy support has been widely studied and described in the literature in Parkinson's disease and other neurodegenerative diseases [17,18,20,22,26-28], but is poorly described in RLS; however, increasingly frequent clinical observations create an interesting perspective for RLS, especially in its forms associated with diabetes [29-33], therefore, it is a tool to be more extensively considered in RLS therapy

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