SENSORY MULTIPLE MONONEUROPATHY INDUCED BY PRAVASTATIN USE: FROM A CASE REPORT TO LITERATURE'S REVIEW

MONONEUROPATIA MÚLTIPLA SENSITIVA INDUZIDA PELO USO DE PRAVASTATINA: DE UM RELATO DE CASO À REVISÃO DE LITERATURA

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ABSTRACT

Statins are frequently prescribed in clinical practice for their proven efficacy in prevention of cardiovascular and cerebrovascular diseases. Despite the recognized beneficial effects of this class of drugs, in recent years, many studies published in medical literature have shown a wide range of adverse effects as a consequence of this therapy, including the risk of peripheral neuropathy. The purpose of this article is to report a case in which clinical features consistent with multiple mononeuropathy probably secondary to use of pravastatin were observed. The case report is followed by a review of the relevant literature.

Keywords: Multiple Mononeuropathy; Peripheral Neuropathy; Statins; Pravastatin

RESUMO

As estatinas são frequentemente prescritas na prática clínica por sua comprovada eficácia na prevenção de doenças cardiovasculares e cérebrovasculares. Apesar dos reconhecidos efeitos benéficos dessa classe medicamentosa, nos últimos anos, diversos estudos publicados na literatura médica vem evidenciando uma ampla variedade de efeitos colaterais como consequência desta terapia, incluindo o risco de neuropatias periféricas. O objetivo deste artigo é relatar um caso no qual foram observadas manifestações clínicas compatíveis com o diagnóstico de mononeuropatia múltipla sensitiva, provavelmente secundária ao uso de pravastatina. O relato de caso é acompanhando de uma revisão de dados pertinentes da literatura.

Palavras-chave: Mononeuropatia Múltipla; Neuropatia Periférica; Estatinas; Pravastatina

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INTRODUCTION

Statins are hypolipidemic drugs widely prescribed in current clinical practice for their proven efficacy in prevention of cerebrovascular and cardiovascular diseases, however, some complications may occur in association with long term use[1]. When considering the wide range of adverse effects secondary to this therapy, statin induced myopathy is recognized as a prevalent condition[2], but other less frequent neuromuscular disorders have been described in medical literature. Recently, growing evidence have pointed to the probable existence of peripheral neuropathy secondary to certain drug-induced biochemical changes due to the inhibitory effect of 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMG-CoA Reductase)[3, 4, 5, 6]. We report a case of a peripheral neuropathy probably induced by pravastatin use.

CASE REPORT

A 54-year-old male hypertense and dyslipidemic patient in use of pravastatin 20mg/day for around two years reported, 30-days prior the consultation, insidious onset of paresthesia of the tingling type in the lateral region of his right foot. The symptoms exhibited a continuous and non-progressive pattern and were not associated with motor deficit, ataxia signs or dysautonomia. No worsening or improving factors were evident. After two weeks, he reported the onset, again insidious, of a similar complaint in the lateral part of the left foot, without irradiation. In this period, no fever, asthenia, weight loss, trauma, cutaneous lesions, joint problems or respiratory complaints were reported. There was no family history of similar clinical conditions. The general clinical exam was unremarkable. Objective neurological exam revealed preserved strength, globally symmetrical and physiological osteotendinous reflexes, normal vibratory proprioceptive sensitivity, and tactile, thermal and pain hypoesthesia in the lateral portion of the right foot. Complementary laboratory exams were normal (Rapid HIV I and II tests, serum VDRL, Serology for Hepatitis B and C, folate, vitamins B12 and D serum levels, complete blood count, erythrocyte sedimentation rate, fasting glycemia, glycated hemoglobin, oral glucose tolerance test, thyroid, liver and kidney functions and urinalysis). While still in use of pravastatin, results of the first nerve conduction study (NCS) were: unexcitable right sural nerve and left sural nerve with low amplitude sensory nerve action potential (Figure 1). The hypothesis of sensory multiple mononeuropathy secondary to statin use was established with subsequent drug withdrawal (pravastatin) and clinical observation. After three months, the patient reported significantly improvement of the previous complaints and repeat NCS (performed by the same examiner, with the same electroneuromyography device) disclosed right sural nerve with reduction in amplitude and slowing of sensitive conduction velocity and left sural nerve with slight slowing in sensitive conduction velocity (Figure 2). The two electromyographies performed were normal.

DISCUSSION

In general, statins (HMG-CoA Reductase inhibitors) are well tolerated and effective in reducing cerebrovascular and cardiovascular risk. However, although uncommon, adverse effects may occur in multiple systems, with involvement of the liver and skeletal musculature being the most serious[7]. The first report suggesting an association between peripheral neuropathy (PN) and statin use was published in 1993[8]. There are now numerous descriptions of cases and population-based studies investigating the existence of this clinical entity[9]. The physiopathogenic mechanism of PN induced by HMG-CoA inhibitors is based on the hypothesis related to certain biochemical reactions, particularly those involved in lowering sera cholesterol and inhibition of the synthesis of Coenzyme Q10 (ubiquinone). Cholesterol is essential for the process of nerve myelination and maintenance of the neuronal cell membrane and is thus important for synaptic activity. Coenzyme Q10 activity reduction affects mitochondrial function, leading to loss of the antioxidant effect which, in physiological conditions, is protective to neurons[10]. Multiple factors can influence the therapeutic response and chance of collateral effects secondary to statin use, such as genetic polymorphism, comorbidities, drug interaction, and particularities of the subclasses of statins[1].

In 2005, in Australia, the Adverse Drug Reactions Advisory Committee (ADRAC) reported having received, since 1993, 281 reports of polyneuropathy probably associated with statin use (the majority associated with sinvastatin and atorvastatin and, less frequently, pravastatin and fluvastatin). Many of these patients had confounding factors for the establishment of the etiology of PN, such as chronic kidney disease and diabetes. However, after statins withdrawal, recovery was seen in around 50% of these cases[11].

A publication of 2006 disclosed that results of an metanalysis involving 4 cohort-type studies[3, 13, 14, 15] revea-

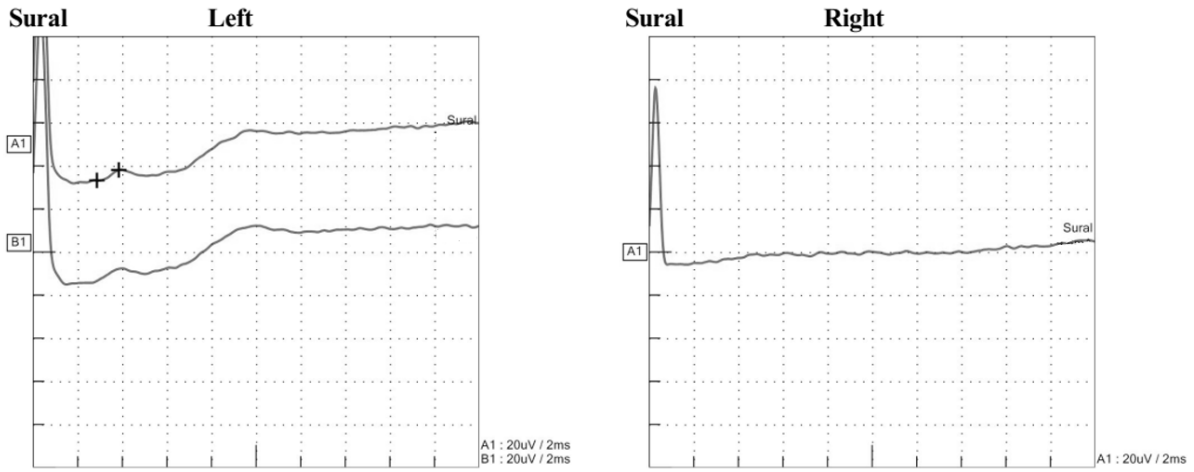

Figure 1 – NCS disclosing reduced sensitive nerve conduction amplitude in left sural nerve (5,2 μV) and absent sensory nerve action potential in right sural nerve (Patient still in use of pravastatin 20mg/day).

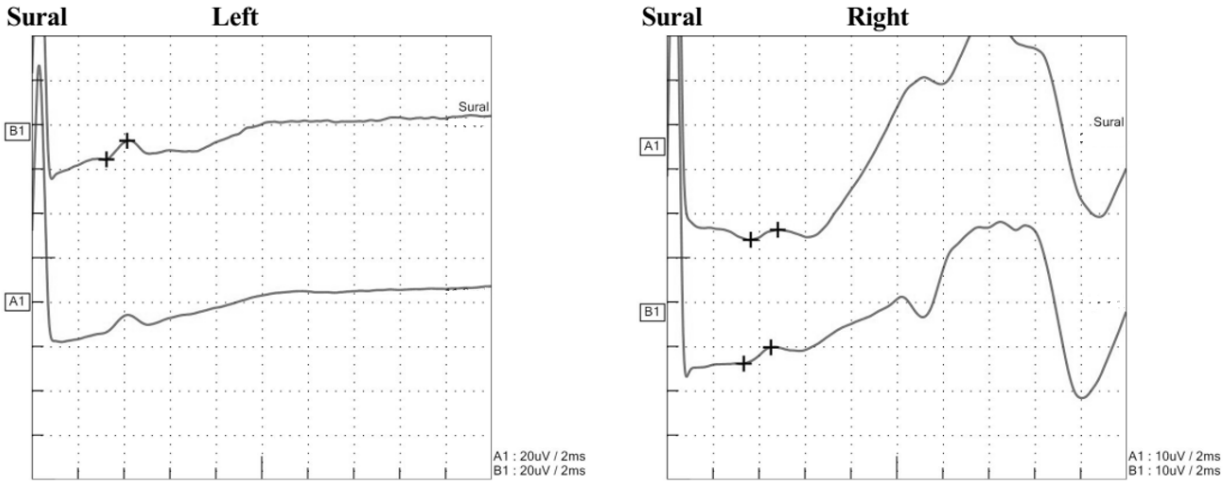

Figure 2 – Sensory NCS disclosing a conduction velocity of 30,2m/s and an amplitude of 9,1μV in left sural nerve, a conduction velocity of 28,8m/s and amplitude of 2,5μV in right sural nerve (three months after withdrawal of pravastatin).

led an odds ratio of 1.8 (95% CI 1.1 – 3.0; $p < 0.001$) for use of statins and risk of peripheral neuropathies (such studies included analysis of PN in research participants taking or not taking those drugs). In the same paper, authors suggested an incidence of 12 cases per 100,000 persons/year and a prevalence of 60 cases per 100,000 persons[12]. Another study suggested a frequency of 4.5 PN cases per 10,000 persons/year in use of statins after excluding other predisposing factors[3].

It has been suggested that the emergence of clinical symptoms consistent with peripheral neuropathic compromise is directly related to the exposure time to the drug and also to the dose used[16]. This association was supported by 16 case reports in which PN symptoms manifested within two months of initiating statins[7,12]. As cited by Henriques et al. in a recent literature review, according different studies, the withdrawal of the drug led to improvement in the clinical condition in most patients where mean (partial or full) recovery time was 61 days (ranging from two weeks to 9 months)[1]. In addition, an inversely proportional relationship between exposure time to statins and probability of complete recovery from PN was observed in some cases[17].

In 2011, Otruba et al. followed 42 patients (23 men – mean age 51.9 years and 19 women – mean age 52.3 years) with defined diagnosis of dyslipidemia and no history of other metabolic disorders or alcoholism. The study participants first underwent neurophysiological study (fibular and tibial nerves – motor nerve conduction velocity, compound muscle action potential, F wave latency; superficial and sural fibular nerves – sensory nerve conduction velocity, sensory action potential). Subsequently, sinvastatin 20 mg/day was prescribed and the neurophysiological assessment repeated at 24 and 36 months. None of the participants reported peripheral neuropathy-related complaints during the follow-up. However, NCS revealed prolonged F wave latency in the fibular and tibial nerves with a statistically significant value ($p < 0.0001$, paired

t-test). The study concluded that long-term statin use may cause clinically silent damage to peripheral nerves when treatment time exceeds two years[18].

Statin-induced PN typically presents as motor-sensitive polyneuropathy with insidious onset[19] and clinical symptoms range from paresthesias, hypo or hyperesthesia of the extremities, hypo or areflexia, motor deficit and dysautonomia[1, 12, 18]. Some more atypical cases possibly associated with treatment using statins have also been reported, characterized by neurological changes resembling Guillain-Barré Syndrome[20], reversible small fiber neuropathy[3] and mononeuropathy multiplex[21, 22]. Regarding treatment, when statin-induced PN is suspected, withdrawal of this class of drug should be considered.

Some authors defend the use of ubiquinone for the management of complications secondary to statin treatment[23,24]. A prospective study suggested benefits of this enzyme (mean daily dose of 240mg/day) for the various adverse effects induced by HMG-CoA reductase inhibitors, including those related to peripheral neuropathy[25]. However, there are few specific studies with high levels of evidence on the use of ubiquinone in the clinical management of statin-induced PN.

We reported the case of an adult middle-aged patient who presented with subacute onset of sensory changes restricted to lower limbs and no reports of other systemic complaints. The exclusion of more common causes of peripheral neuropathy allied with evident clinical and electrophysiological improvement following pravastatin withdrawal leaded us to the most likely hypothesis of statin-induced PN. We believe that the possibility of evaluation bias between the two NCS was reduced by the fact that these complementary exams were performed by the same neurophysiologist, who used the same electroneuromyography device.

Physician should be aware that suspicion for complications associated with the use of HMG CoA-Reductase inhibitors is always valid, given that this drug class is widely prescribed in clinical practice.

CONFLICT OF INTEREST

The authors declares that there is no conflict of interest.

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