Arq Neuropsiquiatr 2004;62(2-B):540-542

SIMVASTATIN-INDUCED MONONEUROPATHY MULTIPLEX

Case report

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ABSTRACT - The association between the use of statins and neuromuscular disease is currently being intensely discussed. We relate a 63 years old man with possible case of statin-induced neuropathy in a patient with dislipidemia in use of simvastatina at high doses. The electrophysiologic studies disclosed findings compatible with mononeuropathy multiplex, suggested by clinical prescutation of asymmetrical numbness and weakness. More common causes of mononeuropathy multiplex were excluded and the patient improved after the discontinuation of the drug.

KEY WORDS: simvastatin, mononeuropathy multiplex, nerve conduction, electromyography.

Mononeuropatia múltipla induzida por sinvastatina: relato de caso

RESUMO - Polineuropatia induzida por estatina é assunto vigente na literatura médica. Relatamos um possível caso de mononeuropatia múltipla induzida pelo uso de sinvastatina em um homem de 63 anos, em uso de sinvastatina. Após o diagnóstico de dislipidemia, iniciou fraqueza e parestesia assimétrica em membros. O estudo eletromiográfico mostrou alterações compatíveis com mononeuropatia múltipla. As causas mais comuns de mononeuropatia múltipla foram descartadas com a realização de exames complementares pertinentes. O paciente melhorou com a descontinuação da sinvastatina.

PALAVRAS-CHAVE: sinvastatina, mononeuropatia múltipla, condução nervosa, eletromiografia.

The widespread use of several drugs in the treatment of lipid disorders has led to the reports of many new side effects previously unknown[1]. Among these lipid-lowering drugs, simvastatin is a potent inhibitor of the hidroximetilglutaril coenzyme A (HMG-CoA) redutase, an enzyme acting in the synthesis of cholesterol. The first reports of peripheral neuropathy due to the inhibitors of HMG-CoA redutase were published in 1994 and 1995[2,3]. Phan and coworkers, in 1995, published a series of four patients with peripheral neuropathy caused by simvastatin, with improvement of symptoms after discontinuing the drug[4]. After these initial reports, other series were published[5], but so far there were no reports of mononeuropathy multiplex due to simvastatin.

We present a rare case of mononeuropathy multiplex, clinical and electrophysiologically confirmed, possible induced by simvastatin with improvement of symptoms after the drug was discontinued.

CASE

A 63 years old man presented with a history of pain in the posterior right thigh that started three weeks prior to his admission. He also developed in a few days paresthesias in his fingers and toes bilaterally, distal weakness in his hands and difficulty to walk. He denied taking alcohol, using illicit drugs or handling chemical substances. He had been taking simvastatin 40 mg a day for the past six months for the treatment of hypercholesterolemia, with an increase in the dosage to 80 mg in the past month due to misinterpretation of his prescription. He also denied taking any other medications or having other systemic symptoms like fever, anorexia or weight loss. Physical examination was normal and on neurological examination he had asymmetric distal weakness of all four members, with the left hand more distinctively compromised, especially the interosseous and abductor pollicis brevis muscles and left foot (Medical Research Council grade 3). The deep tendon reflexes were normal and the plantar response was flexor. He also had diminished tactile sensation in the medial aspect of the left hand as well as in the area corresponding to the peroneal nerve bilaterally, mostly on the left. Vibration sense and proprioception were preserved. The patient walked with left foot drop. Coordination was preserved. Laboratory exams included whole blood count, platelets, electrolytes, renal and hepatic function tests, thyroid hormones, and alkaline phosphatase were within normal ranges. Antinuclear factor, LE cells, anti-neutrophil cytoplas-

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Received 19 August 2003, received in final form 12 November 2003. Accepted 12 December 2003.

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Table 1. Nerve conduction study.

Nerve	Variable Response	Right	Left	N	Nerve	Variable response	Right	Left	N
Median S	Amplitude (μV)	5.0	10.0	>15	Median M	D-Amplitude (mV)	5.3	2.8	>5
	Latency (ms)	3.8	3.5	<3.5		P-Amplitude (mv)	5.2	2.7	>5
	CV(m/s)	34.2	37.1	>49		D-Latency (ms)	11.6	9.4	<4.2
Ulnar S	Amplitude (μV)	18.0	28.0	>15		CV (m/s)	50.9	64.1	>50
	Latency (ms)	2.9	2.4	<3.1		F wave (ms)	37.0	NP	<31
	CV (m/s)	44.8	54.1	>49	Ulnar M	D-Amplitude (mV)	9.5	3.5	>5
Radial S	Amplitude (μV)	15.0	16.0	>12		P-Amplitude (μV)	9.2	3.3	>5.0
	Latency (ms)	2.4	2.1	<2.1		D-Latency (ms)	3.3	3.9	<3.4
	CV (m/s)	58.3	66.6	>50		CV (m/s)	65.3	65.3	>50
Peroneal S	Amplitude (μV)	NP	6	>10		F wave (ms)	29.0	NP	<32
	Latency (ms)	NP	3.5	<3.1	Peroneal M	D-Amplitude (μV)	1.9	1.3	>4.0
Sural	Amplitude (μV)	10.0	10.0	>6		P-Amplitude (μV)	1.8	1.2	>4.0
	Latency (ms)	3.4	3.3	<3.0		D-Latency (ms)	6.9	9.1	<5.6
	CV(m/s)	44.1	42.4	>40		CV (m/s)	51.0	67.5	>40
						F wave (ms)	NP	NP	<55.8
					PoTibial M	D-Amplitude (μV)	8.5	12.3	>5.0
						P-Amplitude (μV)	8.3	13.5	>5.0
						D-Latency (ms)	5.0	4.6	<6.0
						CV(m/s)	43.2	43.7	>40
						F wave (ms)	47.0	47.0	<55.6
						H reflex (ms)	NP	NP	<35

CV, conduction velocity; S, sensory; M, motor; Po, posterior; D, distal; P, proximal; NP, no potentials; N, normal.

mic antibody with cytoplasmic pattern (cANCA), anti-neutrophil cytoplasmic antibody with polynuclear pattern (pANCA), anti-SS A/Ro, anti-SS-B/La, anti Sm, anti RNP/Sm, serum protein electrophoresis, Bence-Jones' protein, creatinekinase, prostate-specific antigen and angiotensin converting enzyme levels were either within normal ranges or negative. Serum antigens for hepatitis B and C viruses and human immunodeficiency virus were also negative. The analysis of the spinal fluid with protein electrophoresis was normal. No Mycobacterium in nerve biopsy was found and a chest x-ray was normal. Electrodiagnostic abnormalites were present, consistent with an mixed axonal and demyelinating sensory-motor mononeuropathy multiplex. Compound motor action potencials were reduced in amplitude in ulnar and median nerves in the left side and peroneal nerve bilaterally. Distal latencies and F- wave latencies were prolongated in bilaterally median nerves. Sensitive action potentials study showed absent right superficial peroneal nerve potential, low-amplitude in left superficial peroneal nerve and in the median nerve bilaterally. Latencies of left and right sural nervs and right radial nerve were slightly prolonged. The nerve conduction velocity had a reduction in sensitive median nerve bilaterally (Table 1). Needle electromyography examination revealed signs of acute denervation with fibrillation potentials and positive sharp waves in the left first dorsal interosseous, left abductor digiti quinti and bilateral extensor digitorum brevis. Voluntary contraction showed reduced recruitment pattern and increasing duration and amplitude of motor unit potential in the left first dorsal interosseous and bilateral extensor digitorum brevis. A biceps muscle biopsy showed signs of both recent and chronic denervation. Sural nerve biopsy was normal. Simvastatin was discontinued and the symptoms started to improve in two weeks, while all the exams were being performed. Despite spontaneous remission of some symptoms after drug discontinuation, corticosteroid treatment with deflazacort 90 mg qid was started, due to a presumptive diagnosis of vasculitis. This diagnosis was later discarded, following the results of the appropriate exams. After one month the patient reported an improvement of strength in both hands and left foot, diminished hypoesthesia of hands and feet. Deflazacort was then titrated to 45 mg qid. Four weeks after the first out-patient visit he no longer had hypoesthesia and had no complaints regarding the use of his hands for daily life activities. Corticosteroids were gradually discontinued during one month. In the last visit, two years after the diagnosis, he remained asymptomatic.

DISCUSSION

Identifying the cause of peripheral neuropathies can be a daunting task, often requiring a plethora of exams given all the different causes of neuropathies. The anatomical classification of peripheral neuropathies, which divides them in focal or generalized groups, also helps in the investigation of the etiology and can also be applied to drug-induced neuropathies. Even though the most common presentation of statin-induced nerve lesion is the generalized form of neuropathy, focal presentations such as in our report should also be considered as individual patients can present with different clinical features, thus suggesting more than one single pathophisiological mechanism[6].

Peripheral nerve damaged associated with simvastatin is probably due to inhibition of mitochondrial HMG-CoA reductase, leading to reduced levels of ubiquinone, an enzyme that plays a key role in the neuronal intracellular production of energy[4, 7]. In statin-induced myopathy a similar mechanism leads to depleted levels of ubiquinone as seen in cultures of cells exposed to lovastatin. Niacin, another lip-lowering drug that doesn't inhibit the synthesis of HMG-CoA redutase, can also induce peripheral neuropathy through a different mechanism, most probably associated with reduction of cholesterol serum levels[7].

Gaist and col.[8] found in a recent case-control study that patients taking statins have a 4 to 14 fold increased risk of developing idiopathic polyneuropathy, when compared to controls. In that study other forms of peripheral neuropathy, such as mononeuropathy multiplex, were not assessed, as the inclusion criteria required that all patients had a clinical and electrophisiogical diagnosis of idiopathic polineuropathy[8]. The main causes of mononeuropathy multiplex are vasculitis, collagen diseases, infectious diseases and diabetes mellitus[9], all of which were discarded in our patient following the results of several exams. We diagnosed his neuropathy as secondary to simvastatin given not only to the time related of the onset of symptoms, since he had been taking the drug for six months with a marked increase of dosage in the last month, but also because sinvastatin can induce a variety of adverse effects described in the literature, raging from psiquiatric[4] to rheumathological symptoms[10]. The improvement of symptoms after the drug was discontinued, as well as remission with corticosteroids treatment, also support our diagnosis of drug-related neuropathy, despite the fact that so far there are no similar reports of simvastatin-induced mononeuropathy multiplex in the literature.

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