

Statins: A Vascular Boon or Muscular Bane?

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I. Introduction

Statins are very fast becoming one of the most frequently prescribed drugs worldwide [1, 2]. Statin therapy is linked to variety of adverse effects especially associated with muscular disorders, the major cause being direct myotoxicity [3]. Statin-associated myopathy represents a broad spectrum of disorders from insignificant myalgia to fatal rhabdomyolysis. The frequent use of the drug has resulted in an increased incidence of statin induced rhabdomyolysis. Most often the condition typically resolves with drug discontinuation, hence the prompt diagnosis of the condition will be life saving [3]. But treating physicians should be aware of different presentations of the condition as some unusual presentation can be misleading and pose difficulty in diagnosis leading to a delay in withdrawing the drug. Here we present two cases of statin induced myopathy both differing in clinical presentation that posed a challenge in diagnosis.

Case Report 1

54 year old gentleman, non-smoker, non-alcoholic, with a previous history of CKD, hypertension and dyslipidemia on conservative treatment, presented to Nephrology department with complaints of muscle pain and progressive weakness of limbs. History and physical examination was suggestive of painful proximal myopathy. There was no history of fever, arthralgia, weight loss, or skin rashes. Medication history revealed long term statins use. For almost a year patient was on atorvastatin, which was replaced with rosuvastatin in view of recurrent myalgia. For blood pressure control patient was being treated with atenolol and amlodipine.

Investigations showed elevated creatine phosphokinase (CPK) of 1268 units/L and serum creatinine of 2.3 mg/dl (similar to previous levels) but liver functions, blood counts and electrolytes were normal. However serum thyroid stimulating hormone (TSH) was elevated (100 IU/L) with low T4 levels suggesting primary hypothyroidism. Nerve conduction study was done which was not suggestive of any nerve involvement.

Patient was withdrawn of statins and further treated with intravenous hydration, thyroxine replacement and supportive care. Patient improved symptomatically and regained normal muscle power within 2 to 3 weeks.

Case Report 2

A 56 year old man, with a recent history suggestive of ischemic heart disease and on aspirin with atorvastatin presented to the department of General Medicine with complaints of severe asthenia and generalized weakness of 3 weeks duration. Patient also gave history suggestive of jaundice and oliguria.

On physical examination, patient seemed to be acutely ill having jaundice, muscle weakness (MRC grade 3) with painful quadreparesis and peripheral edema. Investigations showed cholestatic jaundice, an abnormal renal function (serum creatinine 4.5 mg/dl) with evidence of rhabdomyolysis reflected from elevated creatine kinase levels of 16500 units/dl that rose up to 35400 units/dl over two days. Work up for cause of jaundice including viral markers, ANA, AntiLKM antibodies, serum ceruloplasmin and serum ferritin was normal. Nerve conduction studies done ruled out neuropathy. Muscle biopsy done was suggestive of statin induced myopathy.

Atorvastatin was stopped in this patient, and gradually there was improvement in laboratory indices including serum CPK, renal functions and liver functions. He improved symptomatically and regained his muscle power and general well being.

II. Discussion

Monotherapy with statins are generally well tolerated, and clinical trials reported that the frequency of having an associated adverse event is low. Statins have been the only cholesterol lowering agents having shown mortality benefits so far and this lead to its widespread use. However due to the enormous scale of statin use, incidence of adverse reactions are frequently encountered. The most important adverse effects associated with statin therapy are asymptomatic increases in liver transaminases and myopathy. The spectrum of statin induced myopathy ranges from mild muscle aches (myalgias) to myositis with an elevation of creatine kinase and restriction in mobility, and rarely overt rhabdomyolysis. The estimated frequencies of myalgias, myositis and rhabdomyolysis, as per clinical trials, are 2–11%, 0.5% and <0.1% respectively [4]. However, these clinical

trials have very selectively chosen patients who are at very low risk of having drug associated complications, and this might have led to the misjudgement while estimating the frequency of statin myopathy. Hence it should be noted that contrary to the clinical trials, the prevalence of statin myopathy is definitely more in daily practice and the factors responsible for this may be a combination of interaction between drug, disease, genetics, and concomitant therapy. Some of the established and common risk factors that predispose patients to myopathy are renal disease, liver disease, diabetes mellitus, hypothyroidism, debilitated status, surgery, trauma, excessive alcohol intake, combination therapy with fibrates and heavy exercise [5,6]. The duration of onset of muscle symptoms after starting statin therapy also varies and may occur within weeks in some patients whereas in others it might take several months or even few years. The injury is dose dependent and is reversible after withdrawing the drug, with most recovering within 2 to 3 months.

In the first case reported here, the patient initially was on atorvastatin for almost a year, who after having experienced recurrent myalgias, later switched on to rosuvastatin instead, that precipitated more severe symptoms, including weakness of limbs. As per literature it is quite evident that coexistence of hypothyroidism and CKD combined with statin use was responsible for his myopathic symptoms and establishing a cause here was not a difficult process. But still it needs to be mentioned that, since we don't come across such cases regularly, the diagnosis often get delayed and result in further delay in withdrawal of the drug. Hence it's important to monitor the muscle symptoms and serum CPK in patients with co-morbidities started on statins routinely so as to pick it up at an earlier stage. In some instances, as happened in the second case, if not spotted in the beginning, it may lead to serious complications. Although the second patient recovered due to the timely intervention; the outcome would have been fatal, otherwise. The presence of severe hepatitis and cholestatic jaundice in this case confounded the initial diagnosis owing to the rarity of the presentation. If we search the literature, case reports based on hepatitis associated with statin therapy are very few. Another dilemma encountered in the second case was in determining whether the presence of hepatitis was a complication of statin therapy or was it a pre-existing illness unrelated to it. Determining it was important because, if this was due to the latter one, statin associated rhabdomyolysis can be thought of as a complication precipitated by hepatitis, and hence, finding the cause for hepatitis and treating it would have been necessary. But from history, clinical examination and investigations another cause for hepatitis could not be found. Hence the final conclusion was to attribute both myopathy and hepatitis to statins because literatures quite clearly point out the potentiality of statins to raise the hepatic enzymes, even though incidence of severe hepatitis, as happened in this case, is uncommon.

So it needs to be emphasized that whenever a patient comes with symptoms of muscle involvement, however complex the presentation might be, the statin induced myopathy should be considered if the patient is on statin therapy irrespective of duration of treatment and patient should be withdrawn of statins as soon as possible.

III. Conclusion

Statin induced muscle disease is a common side effect and is frequently missed or reported late due to lack of awareness and poor patient education. Hence it is important for a doctor, not only to recognise muscle symptoms of a patient caused by statins but also to explain it to the patients and ask them to report early in case they occur, so as to prevent serious and often fatal complications.

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