Atorvastatin Induced Myopathy in Asymptomatic Hypothyroidism: Case Report

Asemptomatik Hipotiroidide Atorvastatinle Tetiklenmiş Miyopati

Esra GÜCÜK İPEK[a]

[a]Clinic of Cardiology,
Polatlı Duatepe Hospital, Ankara

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Yazışma Adresi/*Correspondence:*
Esra GÜCÜK İPEK
Polatlı Duatepe Hospital,
Clinic of Cardiology, Ankara,
TÜRKİYE/TURKEY
esragucuk@hotmail.com

ABSTRACT A 46 year old man who has a history of coronary artery disease and hyperlipidemia admitted to our hospital with proximal muscle pain over his extremities during exertion. The creatine kinase level was 3756 U/L upon admission which was thought to be due to 20 mg daily atorvastatin treatment initiated two months ago, after having cardiac catheterization for acute myocardial infarction. The measurements of the thyroid-stimulating hormone (TSH) (75 mIU/mL) and free thyroxine (fT4) (0.3 μg/mL) levels revealed a significant hypotyroidism although patient has no symptom other than myalgia. Atorvastatin was discontinued, he was hidrated by saline infusion and treated with orally thyroxine. Thyroxine replacement, hidration and cessation of the atorvastatin treatment resolved his pain within two weeks while the creatine kinase levels were normalised within two months. This case illustrates the importance of establishing thyroid functions before initating lipid lowering therapy both for exploring a possible seconder hyperlipidemia cause and identifying susceptible individuals for exaggerated side affects of the treatment.

Key Words: Hypothyroidism; muscular diseases; atorvastatin

ÖZET Koroner arter hastalığı ve hiperlipidemi öyküsü olan 46 yaşında erkek hasta proksimal ekstremitelerinde eforla meydana gelen kas ağrısı şikayeti ile hastanemize başvurdu. Başvuru esnasında kreatin kinaz düzeyi 3756 U/L ölçüldü ve bu durumun iki ay önce akut miyokard infarktüsü nedeniyle yapılan kardiyak kateterizasyon sonrası başlanan günlük 20 mg atorvastatin tedavisi nedeniyle meydana geldiği düşünüldü. Miyalji dışında başka bir bulgusu olmayan hastanın tiroid stimulan hormon (TSH) (75 mIU/mL) ve serbest tiroksin (fT4) (0,3 μg/mL) seviyelerinin ölçümü hastada belirgin hipotiroidi varlığını gösterdi. Hastanın aldığı atorvastatin kesildi, serum fizyolojik infüzyonu ile hidrate edildi ve oral tiroksin tedavisi başlandı. Tiroksin replasmanı, hidrasyon ve atorvastatinin kesilmesi ile hastanın ağrısı iki hafta içinde geriledi, kreatin kinaz düzeyleri ise iki ayda normale geldi. Bu vaka lipid düşürücü tedavi başlanmadan önce hem ikincil hiperlipidemi nedenlerini araştırmak hem de tedavinin yan etkilerine maruz kalabilecek hassas bireyleri belirlemek için tiroid fonksiyonlarını göstermenin önemini ortaya koymaktadır.

Anahtar Kelimeler: Hipotiroidizm; kas hastalıkları; atorvastatin

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Hypothyroidism is a well known cause of dyslipidemia.[1] It is also a risk factor for statin-induced myopathy.[2,3] Hence, patients' thyroid status should be evaluated before initiating lipid-lowering medications and when myopathic symptoms are observed in a patient receiving statin therapy, even if the patient lacks classic symptoms of hypothyroidism.[4] This case report presents a patient admitted to our instutution

complaining of muscle pain while recieving 20 mg daily atorvastatin. Eventually he was diagnosed with statin-induced myopathy and unnoticed hypothyroidism.

CASE REPORT

A 46-year-old man admitted to our clinic complaining of muscle pain which had began two weeks ago and persisted. He was experiencing upper and lower proximal extremity muscle pain and cramping during mild to moderate exertion. He had a history of myocardial infarction which was eventually treated by percutaneous coronary intervention two months ago and he was discharged with medications of 100 mg acetylsalicylic acid, 5 mg ramipril, 50 mg metoprolol, 75 mg clopidogrel and 20 mg atorvastatin daily. His physical examination was normal except mild diminished muscle strength and reflexes over his lower extremities. He had no symptom other than myalgia. Serum creatine kinase levels were checked and found to be 3756 U/L (normal range, 0-170 U/L) which were markedly elevated (Table 1). Statin-induced myopathy was suspected, and atorvastatin was discontinued. His thyroid function tests revealed an elevated TSH level of 75 mIU/mL (normal range, 0.4-4 mIU/mL) and a reduced free T4 level of 0.3 μg/mL (normal range, 0.8-1.8 μg/mL) The patient was subsequently given thyroxine replacement therapy and intavenous saline infusion to prevent renal dysfunction. His liver and kidney function tests were within normal ranges. On historical review, the patient denied experiencing any of the classic symptoms of hypothyroidism but after commencing thyroxine treatment, he report an improvement in his daily life energy and attention. His muscle pain was resolved within two weeks. The creatine kinase level decreased to 943 mIU/mL 4 weeks after cessation of the treatment. His thyroid status was markedly improved within 8 weeks (Table 1). We initiated fluvastatin which is a low-potency statin, at a dose of 20 mg daily after 8 weeks of statin free interval. He did not report any muscle cramp or pain and the creatine kinase level was normal on his follow up visits.

DISCUSSION

Hypercholesterolemia and coronary artery disease are both common clinical problems. Statins are widely preferred hypolipidemic agents in those patients to reduce lipid levels and to provide secondary prevention. They are relatively safe but occasionally they may cause severe side effects especially in a subset of vulnerable patients. They in-

TABLE 1: Serum creatine kinase and thyroid hormone levels and medications before and after diagnosis of statin induced myopathy and hypothyroidism.

Date	Creatine kinase (U/L)	Free T4 (μg/mL)	TSH (mIU/mL)	Medications/daily dosage for each
May 2011	288	....	....	100 mg ASA, 5 mg ramipril, 50 mg metoprolol, 75 mg clopidogrel, 20 mg atorvastatin
July 2011	3756	0.3	75	100 mg ASA, 5 mg ramipril, 50 mg metoprolol, 75 mg clopidogrel, atorvastatin stopped, 0.05 mg levothyroxine initiated
August 2011	943	0.5	20	100 mg ASA, 5 mg ramipril, 50 mg metoprolol, 75 mg clopidogrel, 0.1 mg levothyroxine
September 2011	280	1	10	100 mg ASA, 5 mg ramipril, 50 mg metoprolol, 75 mg clopidogrel, 0.125 mg levothyroxine, 20 mg fluvastatin initiated
October 2011	270	1.2	6	100 mg ASA, 5 mg ramipril, 50 mg metoprolol, 75 mg clopidogrel, 0.125 mg levothyroxine, 20 mg fluvastatin

T: Thyroxine; TSH: Thyroid stimulating hormone; ASA: Acetylsalicylic acid.

crease the risk of muscular disorders such as myalgia, myopathy and rarely rhabdomyolysis.[5] In our case the patient was prescribed atorvastatin in a moderately low dosage for seconder prevention. Upon admission due to his musculary pain, we evaluated his creatine kinase and thyroid hormone levels. His kidney functions were normal which ruled out rhabdomyolysis. There was an increase in creatine kinase levels which were greater than ten times the upper normal limit that suggested myopathy.[6] Though he had no symptom related to hypothyroidism, his TSH levels were significantly high.

Hypothyroidism is a cause of seconder hyperlipidemia. It is also a risk factor of statin toxicities. It may induce myopathy and cause creatine kinase elevation by itself alone. For those reasons, in dyslipidemic patients the clinicians should evaluate thyroid hormone and creatine kinase levels before commencing lipid lowering therapies even they are asymptomatic. In our case, the patient had normal creatine kinase levels before having atorvastatin treatment which excluded hypothyroid myopathy.[7] He was on a moderate dose (20 mg) of statin comparing with higher concentrations.[8] He was not using any drug that would cause higher statin serum concentrations and he had no history of a recent trauma and excessive exercise. Finally we conclude that the diagnosis was atorvastatin induced myopathy that was probably exaggerated by hypothyroidism, a known but rare association.[3,7]

Risk factors for statin-induced myopathy include female sex, trauma, vigorous exercise, older age, higher doses of statins, and hypothyroidism.[8,9] Another precipitant factor is genetic polymorphism of the cytochrome P450 isoenzymes which may provoke higher serum statin concentrations.[10,11] Fibrates are also causing myopathy, therefore their concomitant administration with statins raise the risk.[9,12] The exact mechanisms of the statin induced myopathy remains unclear; however possible theories include reduced cholesterol synthesis causing skeletal myocyte membrane instability, mitochondrial dysfunction and coenzyme Q10 deficiency.[13,14] Hypothyroidism itself may induce myopathy and this is thought to be a synergystic interference although exact mechanism is not clearly known.[3,7]

Aches, cramps, and weakness over bilateral proximal muscles are the typical clinical features of statin incude myopathies.[15] Exercise often aggravate the symptoms whereas patients are comfortable at rest.[13,16] Patients diagnosed with statin induced myopathy should be monitorized and stop taking statins. When there is a concomitant hypothyroidism, appropriate management should be given to improve thyroid functions. Statins can be reinitiated once patient become symptom free with normal creatine kinase and thyroid hormone levels. Myopathy related to statins is generally regarded as a class effect, although guidelines suggest that rechallenging with a different statin may be attempted once the myopathy has resolved.[17]

CONCLUSION

We present a patient admitted to our department complaining of proximal muscle pain who was eventually diagnosed with myopathy due to atorvastatin use. We revealed an unknown hypothyroidism which probably exaggerated this adverse reaction. This case report illustrates the importance of thyroid functions in patients receiving statins, as hypothroidism is a risk factor for statin induced musculopathies.

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