Is every case of muscle damage during hypolipemic therapy the side effect of this therapy?

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Abstract: Hypolipemic agents, both statins and fibrates, may cause a spectrum of side effects, including a transient increase in creatine phosphokinase (CPK) activity. Muscle injury may present as common myalgia, non-specific myositis with normal CPK levels, myopathy and in the most serious cases, as rhabdomyolysis. Probability of muscle damage is much more higher in patients with concomittant kidney and liver diseases, hypothyroidism, and serious infections or after some injuries or a heavy physical effort. On the other hand, one of the most common causes of secondary hypercholesterolemia and myopathy is hypothyroidism. This condition, which may enhance the risk of muscle damage in the course of hypolipemic treatment, may sometimes present with an atypical clinical presentation, making its diagnosis challenging. In this article, we present the case of a 50-year-old male physical worker presented with marked dyslipidemia, in whom myopathy was diagnosed during therapy with hypolipemic agents. Cessation of the treatment resulted only in a moderate reduction of CPK activity. Only just the introduction of thyroid hormone supplementation led to regression of symptoms and normalization of abnormalities found in laboratory examinations including remarkable improvement in lipid profile. After several months of observation we consider that hypolipemic treatment probably revealed the previously occult autoimmune thyroid disease in this patient.

Key words: creatine phosphokinase, fibrates, hypothyroidism, myopathy, statins

INTRODUCTION

Hypolipemic agents, both statins and fibrates, may cause a number of side effects, including particularly the transient increase in aminotransferases and, uncommonly, creatine phospohokinase (CPK). Muscle injury may present as transient myalgia, non-specific myositis with normal CPK, myopathy and, occasionally, rhabdomyolysis [1,2]. Its occurrence may be caused by renal insufficiency, hypothyroidism, severe injury, infections or ischemia [3-6]. Other risk factors are older age, female sex, high dose statin administration [7]. Probability of rhabdomyolysis is higher when combined therapy with statin and fibrate is provided or when other cytochrome P450 inhibitors, especially those of isoenzyme 3A4, are used [3,5,7,8]. The risk while on multi-drug therapy is estimated to be increased by 2%, while in monotherapy the risk of severe myopathy is about 0.08% [8].

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Dyslipidemia is one of major risk factors for cardiovascular disease which can be modified by diet and hypolipemic agents. However, if this medication is administered secondary hyperlipidemia causes, e.g. improperly controlled diabetes, kidney disease, liver disease, alcoholism and hypothyroidism, should be taken into account [4].

When lipid disorder is present, exclusion of hypothyroidism seems to be particularly important. Coexistence of hypothyroidism predisposes to myopathy or rhabdomyolysis while on hypolipemic agents and concurrently it is a common cause of secondary hyperlipidemia and myopathy. However, thyroid hormone substitution usually leads to normalization of lipid profile and muscle damage indicators like CPK or aldolase [4,9-11].

CASE REPORT

In this paper we present the case of a 50-year old male patient with severe dyslipidemia diagnosed in 2004 during preventive checkup tests, initially treated with simvastatin 40 mg daily and then with combined therapy with fibrate (lovastatin 20 mg + fenofibrate 100 mg daily). In May 2005 the patient was admitted to the Internal Ward due to unclear stomach complaints with concomitant elevated aminotrans-

ferases. The ultrasonography showed mild hepatomegaly and hyperechogenic liver. In the liver biopsy hepatic steatosis with micro- and macrovesicular fatty degeneration and slight pericellular fibrosis was confirmed. Hemosiderin staining was negative. Viral hepatitis was excluded and hypolipemic therapy was modified; the treatment was continued with fibrate only (micronized fenofibrate, 267 mg daily).

In December 2006 lumbar pain occurred and was considered to be related to physical work. The patient was treated with tolperisone and oral diclofenac without improvement. Moreover, mild generalized muscle pain with proximal weakness of lower limbs, paresthesias, and the sensation of cold in distal parts of limbs with impaired sense in the hands and feet occurred. Laboratory tests results: CPK 7599 U/l; C-reactive protein (CRP) 1.0 mg/l; triglycerides (TG) 327 mg/dl; cholesterol 346 mg/dl, low-density lipoprotein (LDL) 228 mg/dl; alanine aminotransferase (AlAT) 139 U/L. All the medications, including fenofibrate were withdrawn. The patient was referred to the Department of Internal Diseases and Clinical Pharmacology, Medical University of Silesia, Katowice, with a suspicion of skeletal muscle degeneration in the course of hypolipemic treatment.

On physical examination livedo reticularis and dermographism all over the body were observed. The skin of lower limbs was dry with feet cracks. The feeling of increased muscle tension of that region was reported; moreover, difficulties in pulse evaluation on lower limbs appeared. The heart rate was regular – 60/min, blood pressure 130/80 mmHg.

The patient reported a change in stool appearance (loose, watery stool, 3–5 times a day), drenching night sweats, weight gain (12 kg/year) and sexual dysfunction. The medical history revealed laparoscopic cholecystectomy (2000) and umbilical hernia surgery (2005). The patient did not smoke for 12 years, used alcohol occasionally, but observed intolerance to high-proof spirit for a couple of months.

On admission to the Central Clinical Hospital in Katowice (February 2007) laboratory tests revealed: CPK 4230 U/l, aldolase 38 U (N 5–25 U) AlAT 119 U/l, aspartate aminotransferase (AspAT) 119 U/l, γ-glutamyl transpeptidase 34 U/l, alkaline phosphatase 45 U/l, bilirubin 0.72 mg/dl, lactate dehydrogenase 469 U/l, creatinine 1.1 mg/dl, CRP 1.01 mg/l, no abnormalities in protein fraction pattern, ionogram, blood coagulation test, urine test and peripheral blood cell count. Connective tissue disease tests (anti-nuclear, anti-mitochondrial, anti-smooth muscle and liver/kidney microsomal antibodies) were negative; prostate specific antigen, carcinoembryonic antigen and α-fetoprotein remained normal, as well as glucose tolerance test. Thyreotropic stimulating hormone (TSH) was 93 μIU/ml (N 0.35–4.94), free tyroxine (FT4) <0.4 ng/dl (N 0.7–1.48). Thyroid peroxidase antibody 324 IU/ml (N ≤12), thyreoglobulin <0.2 ng/ml (N ≤55), gastric parietal cell antibody test – positive (with normal vitamin B_{12} and folic acid serum levels). The electrocardiogram (ECG) – normal; the electromyogram (EMG), panendoscopy, colonoscopy – normal; the Doppler sonography of carotid arteries – normal; the abdominal sonography – hepatic steatosis; the sonography of the thyroid gland – a reduced size of thyroid lobes, with no focal lesions. In the color Doppler sonography an increased rate of blood flow mainly of the left lobe was observed. The fine needle biopsy of the thyroid gland confirmed the diagnosis of chronic lymphocytic thyroiditis.

The patient was diagnosed with autoimmune Hashimoto's thyroiditis with myopathy. Coexistence of autoimmune thyroiditis and gastric parietal cell antibodies could suggest type 2 or 3 multiglandular autoimmune syndrome. That was excluded with normal corticotropin, cortisol and aldosterone and a normal peripheral blood count. The patient was treated with levothyroxine with an initial dose of 75 μg which was gradually increased. After 10 days of treatment previously reported symptoms partially resolved and a decrease in biochemical parameters was observed (CPK from 4230 to 1590 U/l; TSH from 93 to 69 μIU/ml; FT4 from <0.4 to 0.86 ng/dl; AlAT from 119 to 95 U/l; AspAT from 119 to 89 U/l; total cholesterol from 380 to 250 mg/dl; LDL from 254 to 165 mg/dl; TG from 365 to 260 mg/dl). The patient was referred to the outpatient Clinic of Metabolic Diseases. After 6 moths the patient remained asymptomatic with laboratory tests results: TSH – 1.214 μIU/ml and CPK – 1002 U/I and lipid profile comparable with that on discharge from hospital.

DISCUSSION

Hypothyroidism as a secondary cause of dyslipidemia is not difficult to diagnose once clinical presentation is characteristic. The diagnostic difficulty occurs when clinical presentation is not complete with leading symptoms which incline a patient to consult with other specialists. Stiffness and weakness with accompanying muscular hypertrophy due to hypothyroidism is called the Hoffman syndrome [12-14]. If muscular symptoms are predominant this is called *polymyositis- like syndrome* [15-17] because the clinical presentation resembles polymyositis. In the case described in the present paper no other symptoms of hypothyroidism than muscle damage, dyslipidemia, weight gain and skin lesions were observed, and some symptoms (drenching sweats, frequent bowel movements) were even against that diagnosis. That is the reason why hormonal assessment of the thyroid gland is needed in every case when muscle damage of unclear origin occurs even if clinical presentation is not typical. Since there are some reports of mild skeletal muscle dysfunction in the subclinical phase of hypothyroidism available, hormonal assessment should include not only thyroid hormone levels, but also TSH. Despite significant CPK elevation, the patient reported only slightly pronounced muscle pain. The fact confirms the need for routine CPK testing in every case of hypothyroidism [2].

Because the decrease in CPK activity was rapid and pronounced not until hormonal thyroid function was normalized, it should be assumed that thyroid gland insufficiency is the primary and evident cause of the observed muscle dysfunction.

The peak of CPK activity occurred while the patient was receiving hypolipemic treatment, and was reduced by half after fibrat withdrawal, which shows that the treatment intensified damage of muscle and could reveal pathologic process that was previously present.

Available data show other similar cases when generalized muscular disorders of different intensity after fibrates or statins introduction contributed to the diagnosis of thyroid gland disorder [10,11,17,19]. Different clinical appearances of muscle damage may be caused by coexistent factors: exertion, liver or renal failure, hormonal disorders or even common viral infections [3]. The course of Hashimoto disease, which is the cause of thyroid gland insufficiency, is chronic and therefore the explanation that thyroid disease is a factor that intensifies muscular toxicity of hypolipemic therapy is less probable.

Hypothyroidism is a disease of heterogenous and individually varying clinical presentation, thus an appropriate diagnosis is crucial to adequate treatment introduction. The case described and other available case reports [4,9,11] demonstrate that L-thyroxin substitution usually leads to symptoms resolving and CPK normalization and, in the majority of cases, to normalization of lipid profile. In the case presented the period of time between dyslipidemia and diagnosis of hypothyroidism was three years. This suggests that thyroid functional tests should be performed in every case of severe dyslipidemia and in patients resistant to standard therapy before treatment modification. On the other hand, when multi-drug treatment is needed, each side effect should be carefully monitored because only the post-clinical data show the whole toxicity drug profile, not narrowed to the limited clinical trial follow-up only.

The case described above demonstrates that in some hypothyroidism cases with incomplete clinical demonstration, the accurate diagnosis may be significantly delayed despite major abnormalities in the hormonal profile. Our observation shows that hypolipemic therapy may reveal an autoimmune reaction in the thyroid gland and increase hypothyroidism-associated myopathy.

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