To physicians, it appeared that the patient surely had Graves’ disease, but this was not the case. Several months before his admission to the Endocrinology Department, a 48-year-old man developed rapidly growing eyelid swelling, the feeling of having sand in his eyes, redness of the conjunctivae, diplopia, and photophobia. He worked as a driver, so the symptoms kept him from his job, and made other everyday activities truly difficult. Neither a family nor personal history revealed any thyroid disease. The patient did have a history of combined hyperlipidemia (Table 1), which had been treated with fenofibrate, 267 mg daily, for 8 years. Atorvastatin, 10 mg every night, had been added 7 months before the current hospitalization. (The patient and the local Committee on Human Research approved publication of this report.)

ASSESSMENT

An ophthalmologic examination revealed severe bilateral palpebral swelling and right-sided exophthalmos; conjunctival injection, chemosis, and lacrimal caruncle edema were present in both eyes (Figure 1A). Visual acuity was normal (20/20) in both eyes. Pupils were equal, round, and reactive to light. The intraocular pressure was normal in both eyes, and ocular media were clear. Bilateral fundus examination indicated that the disc, vessels, macula, and peripheral retina were within normal limits in each eye. However, the patient had significant horizontal diplopia, and the interpalpebral fissure was narrowed on the left.

He also had up-gaze limitation and slightly limited abduction and adduction in both eyes. The Möbius sign (inability to maintain convergence of the eyes) and Stellwag’s sign (infrequent blinking) were bilaterally positive. Lid lag (von Graefe’s and Kocher signs) was slightly expressed on the right. According to the NO SPECS classification (0, No signs or symptoms; 1, Only signs, no symptoms; 2, Soft tissue involvement; 3, Proptosis; 4, Extraocular muscle involvement; 5, Corneal involvement; 6, Sight loss) of Graves’ orbitopathy, established by the American Thyroid Association, the patient presented with 4th-class ophthalmopathy, and he scored 6 points in the 7-point Clinical Activity Scale.

Physical examination revealed no goiter or clinical signs of hyperthyroidism, such as fine tremor of the hands, tachycardia, or exaggerated deep-tendon reflexes. Surprisingly, biochemical tests showed normal thyroid function and negative antithyroid autoantibodies (antithyroid peroxidase, antithyroglobulin, and antithyroid-stimulating hormone receptor autoantibodies). However, he did have elevated levels of alanine aminotransferase (98 U/L), aspartate transaminase (110 U/L), and creatine phosphokinase (352 U/L).

Magnetic resonance imaging (MRI) of the orbits exhibited bilateral exophthalmos, tendon-sparing extraocular muscle enlargement, and an enhanced signal in the short T1-inversion recovery sequence. Infiltration of the fat body of the orbit also was present (Figure 2, A and B). The lacrimal glands were not enlarged, and the ocular nerves were uncompressed.

DIAGNOSIS

An ophthalmologist and a radiologist both believed the clinical diagnosis was active Graves’ orbitopathy. However, the patient had been admitted to the endocrinology ward 5 months after the emergence of ocular symptoms. Repeated laboratory tests confirmed biochemical euthyroidism and negative antithyroid autoantibodies. Moreover, ultrasound of the thyroid indicated the gland was of normal size and echogenicity. This also was supported by the results of laboratory tests (Table 1). The concentrations of alanine aminotransferase, aspartate transaminase, and creatine phosphokinase were slightly elevated. Levels of total pro-
tein, creatinine, and C-reactive protein were normal, as was the erythrocyte sedimentation rate. Antinuclear or antineutrophil cytoplasmic antibodies were not present. Rheumatoid factor and anticyclic citrullinated peptide antibodies were negative. The results of the Mantoux and Schirmer’s tests also were negative. MRI of the brain revealed no abnormalities.

After ruling out other potential causes of the patient’s symptoms (Table 2), an adverse drug reaction to the patient’s atorvastatin therapy was suspected. Four weeks after the withdrawal of both antihyperlipidemic drugs, all of the patient’s eye symptoms resolved. Ocular motility became normal, and he had no ptosis, eye redness, or diplopia (Figure 1B). Spectacular improvement was confirmed by MRI (Figure 2, C and D). Additionally, a complete normalization of creatine phosphokinase levels and liver aminotransferases was observed. Thus, the patient was diagnosed with statin-induced extraocular muscle myopathy. Figure 3 depicts a time relationship between the symptoms and medical interventions.

Statins are among the most widely prescribed medications worldwide. A number of randomized clinical trials have proven their safety and efficacy in prevention of major cardiovascular events. Muscle symptoms are the most common adverse effect of statin therapy, with an estimated prevalence of 10%-15% of treated patients. The spectrum of statin-induced myopathy ranges from common and benign myalgia, through weakness and asymptomatic creatine phosphokinase elevation, to rare but life-threatening rhabdomyolysis. Here we report a case of reversible statin-induced extraocular muscle myopathy that mimicked Graves’ orbitopathy and resolved fully after treatment withdrawal.

A literature search revealed only 3 case reports of eye-muscle myopathy related to statin therapy. However, a recent comprehensive analysis of reports from the National Registry of Drug-induced Ocular Side Effects, World Health Organization, and Food and Drug Administration revealed 256 cases of statin-induced ophthalmologic side effects. Still, it is probable that eye muscle symptoms occur much more frequently than are actively reported or recognized. The median time from the beginning of therapy to the appearance of an adverse drug reaction was 3.5 months. Ocular symptoms were most often associated with the use of Statins and Fenofibrate in a patient with Hyperlipidemia.
administered with statins. However, patients on combined statin and fibrate therapy are at a higher risk of developing myopathic adverse effects because both drugs are associated with muscle-targeted toxicity. It also has been demonstrated that coadministration with fibrates enhances atorvastatin-induced myopathy, although atorvastatin causes little apoptosis alone. Moreover, statins and fibrates synergistically aggravate rhabdomyolysis. The etiological background of this phenomenon remains unexplained, but one of the suggested mechanisms is concomitant action of both drugs on chloride conductance and sarcolemma excitability. However, there are no data on the influence of concurrent use of statins and fibrates on the incidence of extraocular muscle myopathy.

The relationship between statin therapy and symptoms related to extraocular muscle involvement is feasible. This causality assessment is based on the timing of drug administration and the subsequent adverse drug reaction, as well as multiple reports of positive dechallenge and rechallenge. Why some patients experience the symptoms of myopathy in the extraocular muscles alone remains unexplained. One of the suggested etiologies is localized myositis. Another mechanism might be statin-induced peripheral neuropathy. In such cases, a careful differential diagnosis that includes euthyroid Graves’ disease ought to be constructed. The evident temporal relationship of the initiation of statin therapy with the onset of the symptoms and resolution with the cessation of antihyperlipidemic treatment argue against the role of antithyroid-stimulating hormone receptor antibodies in etiopathogenesis of ophthalmologic symptoms in these patients. Additionally, changes in the creatine phosphokinase level suggest muscle toxicity, as Graves’ disease does not cause creatine phosphokinase elevation itself. This strongly implies that the relationship between statin therapy and ocular symptoms is that of cause and effect rather than being coincidental.

**MANAGEMENT**

Our patient had combined hyperlipidemia, which had been treated with a combination of fenofibrate (267 mg/24 hours) for 8 years and atorvastatin (10 mg/24 hours) for the previous 7 months. After ruling out other potential causes of the complaints, his lipid-lowering drugs were withdrawn. Upon resolution of ophthalmologic symptoms, fenofibrate was reintroduced. The patient, whose observation period has now reached 1 year, continues to be followed in an endocrine outpatient clinic. He remains constantly euthyroid, with no clinical or laboratory features of Graves’ disease and no relapse of ocular symptoms. His lipid profile did not worsen significantly with statin withdrawal. Actually, it improved once the patient returned to fenofibrate monotherapy. The most probable reason for this discrepancy: the patient’s fair compliance with pharmacological treatment was undermined by poor adherence to dietary recommendations. After another session of extensive counseling on the role of lifestyle change, his compli-
### Table 2  Differential Diagnosis for the Patient’s Symptoms

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Graves’ Disease</th>
<th>Wegener’s Granulomatosis</th>
<th>Tuberculosis</th>
<th>Sarcoidosis</th>
<th>Sjogren’s Syndrome</th>
<th>Renal Insufficiency</th>
<th>Hypoproteinemia</th>
<th>Brain Tumor</th>
<th>Statin-induced Extraocular Muscle Myopathy</th>
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<tr>
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<td>Tendon-sparing extraocular muscle enlargement, elevated signal in STIR sequence, lack of extraorbital extension</td>
<td>Pseudotumor of the orbit, extraorbital extension</td>
<td>Pseudotumor of the orbit, extraorbital extension</td>
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<td>N</td>
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<td>Brain tumor, increased intracranial pressure, elevated signal in STIR sequence, lack of extraorbital extension</td>
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</table>

ALT = alanine aminotransferase; AST = aspartate transaminase; c-ANCA = cytoplasmic antineutrophil cytoplasmic antibodies; CPK = creatine phosphokinase; MRI = magnetic resonance imaging; N = normal value; p-ANCA = perinuclear antineutrophil cytoplasmic antibodies; STIR = short T1-inversion recovery; TRAb = antithyroid stimulating hormone receptor antibodies; TSH = thyroid stimulating hormone; ↓ = decreased value; ↑ = increased value; + = positive.
ance with dietary suggestions improved. Moreover, because his severe adverse drug reaction precluded use of statins, other possible interventions needed to be intensified if his elevated cardiovascular risk was to be reduced.

The patient continued on fenofibrate monotherapy as well as a Mediterranean and low-fat diet. Two months after atorvastatin was withdrawn, when his lipid profile remained unsatisfactory, he was additionally given a fish-oil preparation containing 465 mg of eicosapentaenoic acid and 375 mg of docosahexaenoic acid and told to take 4 g daily. To conclude, an isolated form of extraocular muscle myopathy ought to be considered in patients on statin therapy when they present with ophthalmologic symptoms mimicking Graves’ disease.

References

Figure 3  This scheme depicts the time relationship between symptoms and medical interventions.