Case Report

Statin-induced bilateral foot drop in a case of hypothyroidism

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Abstract

Muscle involvement is a common manifestation of both clinical and subclinical hypothyroidism, with serum creatine kinase (CK) elevation being probably the most common manifestation, and is seen in up to 90% of patients, but is usually mild (less than 10 times the upper limit of normal). Rhabdomyolysis is a distinctively uncommon presentation of hypothyroidism described usually in the setting of precipitating events such as strenuous exercise, alcohol, or statin use. Rarely rhabdomyolysis and myoedema seen in hypothyroidism can be complicated by the development of anterior compartment syndrome leading to neurovascular compression. We describe a case of a patient with hypothyroidism who developed acute onset bilateral foot drop on initiation of statins. This case highlights the need for cautious use of statins in patients at risk for rhabdomyolysis.

Key Words

Anterior tibial compartment syndrome, foot drop, statins

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Introduction

A variety of central and peripheral nervous system manifestations are common in patients with hypothyroidism. Muscle involvement is a common manifestation of hypothyroidism and its severity may vary from asymptomatic elevation of serum creatine kinase (CK) to disabling muscle weakness.[1] Rhabdomyolysis is a rare but important neuromuscular complication of hypothyroidism and is usually precipitated by strenuous exercise or statin use.[2,3] Rhabdomyolysis can cause a number of systemic complications, most notably acute renal failure. In addition rarely, muscle edema and rhabdomyolysis can cause increased pressure in the anterior tibial compartment resulting in neurovascular compression. We describe a patient with acute onset bilateral foot drop as a result of acute anterior tibial compartment syndrome (ATCS) in the setting of uncontrolled hypothyroidism and statin use.

Case Report

A 51-year-old male presented to us with complaints of acute onset bilateral foot drop of 1-dayduration. On detailed evaluation he came out with a history of hoarseness of voice for 2 months prior to the onset of foot drop. He described that his voice had become heavy and thick, making it difficult for others to understand him. He was investigated and was found to have hypothyroidism (thyroid-stimulating hormone (TSH) = 112.42μIU/ml) and his lipid profile was deranged, with elevated serum cholesterol (428 mg%) and low-density lipoprotein (LDL) cholesterol (348 mg%) for which he was prescribed levothyroxine (LT4; 50 μg/day) and atorvastatin (40 mg/day) by a private practitioner. One week into the treatment he developed severe pain in his legs which was predominantly localized in the shin along with swelling and redness and within 4 days of this pain he developed sudden onset weakness in both feet in the form of being unable to move his toes and had difficulty in clearing his feet off the ground, for which he presented to our hospital. He denied any history of unusual or excessive exercise, fever, or having taken alcohol. On examination at the time of admission, his vital were stable with a pulse rate of 62/min and blood pressure of 110/72 mmHg. Non-pitting edema with overlying erythema was present on both legs without any muscle wasting and both dorsalis pedis were well palpable. Neurological examination revealed weakness of dorsiflexion at ankle joint (Medical Research Council (MRC1/5)) and eversion at subtalar joint (MRC1/5) with normal inversion, thereby, suggesting bilateral common peroneal palsy. Deep tendon reflexes were normal except ankle reflex which was absent. Other than loss of vibration at big toe, sensory examination was unremarkable.

Hemogram revealed hemoglobin concentration of 12.7 g%. The white blood cell count was 16,700 cells/mm^3 with 84%

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polymorphs and toxic granules. Kidney function tests and serum bilirubin were normal, but serum glutamic oxaloacetic transaminase (SGOT) and serum glutamatepyruvate transaminase (SGPT) were mildly elevated (91 and 122 IU/L, respectively). Creatine phosphokinase (CPK) was markedly raised at 6,459IU/L. Free triiodothyronine (T3;1.50 pg/ml) and free thyroxine (T4;0.557 ng/ml) were low and TSH was raised markedly (49.53 μIU/ml). Nerve conduction studies revealed extremely low amplitudes in left common peroneal nerve, while right common peroneal was nonexcitable. Other than markedly reduced compound muscle action potentials in both common peroneal nerves, nerve conduction studies were normal. An ultrasound of the legs revealed bulky superficial muscles of anterolateral aspect of right leg with loss of normal fibrillarypattern and ill-defined hypoechoic areas. Magnetic resonance imaging (MRI) of the legs revealed heterogeneous hypointense signal on T1-weighted imaging (T1WI) and a hyperintense signal on T2-short tau inversion recovery (STIR) weighted images in the anterior and lateral compartment muscles with loss of striations which was consistent with swelling, inflammation, and necrosis of these muscles [Figure 1]. A diagnosis of hypothyroidism with severe myopathy with rhabdomyolysis and acute ATCS causing bilateral common peroneal nerve palsy was made. Atorvastatin was stopped, and patient was continued on LT4 with subsequent improvement in the pain and swelling of the legs, but there was only minimal improvement in the weakness of the feet.

Discussion

Muscle involvement is a common manifestation of both clinical and subclinical hypothyroidism.[1] Symptomatic muscle disease, however, is less common. Myopathymay develop concurrently with hypothyroidism or may prefacebiochemical hypothyroidism.[4] The clinical features of hypothyroid myopathy include weakness, cramps, aching or painful muscles, sluggish movements and reflexes, and myoedema (mounding up of the muscle on percussion).[5] There may also be an increase in muscle bulk. CK elevation, although common is usually less than 10 times the upper limit of normal in hypothyroidism.[1] Rarely rhabdomyolysis associated with hypothyroidism, in some cases leading to renal failure has been reported in literature as well.[6] This may occur spontaneously or may be precipitated by strenuous exercise, alcohol consumption, or use of statins as was seen in our case as well. Clinically patients present with a classical triad of muscle pain, weakness, and dark urine; though more than half of patients may not report muscular symptoms or dark urine.[7] Although the CK level does not correlate with the severity of the myopathic process, but CK levels greater than 1,500 IU/L are usually associated with rhabdomyolysis as was seen in our case.[8] The other characteristic finding seen in rhabdomyolysis is the reddish-brown discoloration of urine because of myoglobinuria. This may be observed in only half of cases because filtered load of myoglobin may be insufficient or has largely resolved before the patient seeks medical attention due to its rapid clearance as may have happened in our case. Complications include fluid and electrolyte abnormalities, hepatic injury, cardiac dysrhythmias, acute kidney injury, disseminated intravascular coagulation, and compartment syndrome.[9] ATCS as a complication of rhabdomyolysis secondary to hypothyroidism is a rather rare condition. ATCS is most commonly unilateral. Bilateral involvement though seen is rare and present only in around <10% of cases.[10] ATCS can result from causes that decrease the size of the compartment or by those increasing its contents. In hypothyroidism, several factors may be conducive to the development of ATCS. The contents of the anterior tibial compartment can increase because of interstitial edema and in some cases from true muscle hypertrophy. Skeletal muscle hypertrophy occurs in 1% of cases of myxedema myopathy and is referred to as Hoffman's syndrome in adults and as Kocher-Debre-Semelaigne syndrome in infants and children.[11] In our case also there was radiological evidence of enlargement of muscles of the anterior compartment with loss of fibrillary pattern resulting in increased compartment size and compression of the neural structures. Additionally, extravasation of protein-rich fluid in the interstitium because of an increase in the capillary permeability and slow lymphatic drainage can also result in increasing the size of the compartment.[12] A decrease in the compartment size can occur because of connective tissue proliferation in myxedema, and thus contribute to the development of ATCS which could cause compression of the deep peroneal nerve and resultant foot drop.[13] Alternatively, deposition of glycosaminogly cans in the perineural sheath of the deep peroneal nerve could also be responsible for the bilateral symmetrical foot drop observed in our patient.[5] Yasuoka *et al*., had reported a case of unilateral deep peroneal nerve palsy associated with hypothyroidism which recovered completely with LT4 replacement. They postulated that focal edema and glycosaminogly can deposition in the perineural sheath was responsible for the reversible conduction block of the deep peroneal nerve.[14]

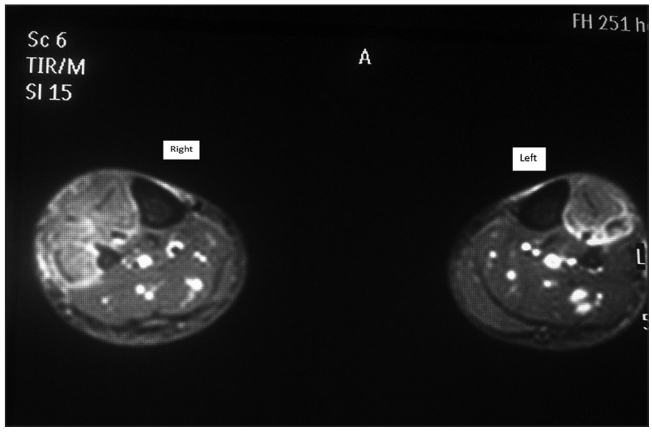

Figure 1: Axial T2-STIR weighted images of legs showing heterogeneous hyperintense signal in the tibialis anterior and peronei on the right side and tibialis anterior on left side. STIR = Short tau inversion recovery

ATCS in the setting of uncontrolled hypothyroidism was first reported by Thacker *et al*., in 1993.[15] ATCS complicating rhabdomyolysis in the setting of hypothyroidism is distinctly rare and to our knowledge there are only five case reported so far [Table 1]. Although surgical release has been tried in ATCS associated with hypothyroidism, it has not been much rewarding and conservative management has yielded similar

Table 1: Summary of cases of anterior compartment syndrome complicating rhabdomyolysis in patients with hypothyroidism

Authors	Nation	Age/sex	CPK (IU/L)	TSH	Precipitating factor	Management
Thacker *et al*.[15]	India	40/M	NA	118	None	Faciotomy
Bhansali *et al*.[16]	India	41/M	80,730	58.9	None	Conservative
Muir *et al*.[17]	New Zealand	22/M	25,000	>100	Adrenal insufficiency	Conservative
Hsu *et al*.[18]	United States of America	33/F	11,319	87	None	Faciotomy
Ramdass *et al*.[19]	United Kingdom	54/M	6,000	63.2	Simvastatin	Faciotomy

CPK = Creatine phosphokinase, TSH = Thyroid-stimulating hormone, M = Male, F = Female

results, unlike traumatic ATCS in which surgical decompression has consistently yielded good results.[17]

Our patient had symptoms of hypothyroidism and investigations revealed an altered lipid profile, because of which he was started on atorvastatin along with LT4. The addition of lipid lowering agents in a patient predisposed to myopathy can have disastrous consequences as was evident in this case. It is important to realize that hypothyroidism itself can be responsible for dyslipidemia. In fact American Thyroid Association recommends that patients with newly diagnosed hyperlipidemia be screened for hypothyroidism prior to starting a lipid-lowering agent.[20] In addition, hypothyroidism is a known risk factor for statin-induced myopathy.[21] It is pertinent that all patients with hyperlipidemia associated with overt hypothyroidism be treated with LT4 therapy first before starting statins, because 4-6 weeks of replacement therapy may correct dyslipidemia in patients with overt hypothyroidism. This is necessary because it has been observed that these patients often have a poor therapeutic response to satins and concomitant use of lipid-lowering drugs with LT4in such patients carries a higher risk of myopathy including rhabdomyolysis as was evident in our patient. If the lipid profile remains deranged after 4-6 weeks of LT4therapy, lipid-lowering medications may be started if the TSH levels have become normal.[22] Even then it is necessary to keep an eye for symptoms of myopathy since rhabdomyolysis and its complications can be a cause of severe morbidity and mortality.

To conclude, anterior compartment syndrome (ACS) and rhabdomyolysis are rare complications of hypothyroid myopathy. In the present era, when use of statins is highly prevalent, physicians should be aware of this complication of statin use in patients with hypothyroidism. Two important clinical learning points are emphasized by this case. Firstly in patients with overt hypothyroidism, LT4 therapy alone may be sufficient to correct dyslipidemia and use of statins in uncontrolled hypothyroidism may be deleterious even when used in combination with LT4. Secondly, hypothyroidism should be ruled out in cases of spontaneous nontraumatic anterior compartment syndrome. It is important to be aware of these complications because early diagnosis can help in preventing unnecessary surgical therapy and potential disability.

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