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Elevation of Creatine Kinase during Medical Treatment of Graves' Disease

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Hyperthyroidism is a pathological syndrome in which tissue is exposed to excessive amounts of circulating thyroid hormone. Antithyroid drugs (ATDs) are one of the therapeutic strategies for this condition. However, common side effects include skin rash, urticaria, and rarely, elevated serum creatine kinase (CK). We describe 2 cases of increases in serum CK concentrations in patients undergoing treatment of Graves' disease with ATDs. Presenting complaints consisted of myalgia and muscle cramps in both patients, and increases in serum CK levels were noted a few weeks after initiation of ATD treatment. At the time of CK elevation, both patients were in subclinical hyperthyroidism. While the mechanisms for this effect are not yet clear, it is likely that acute decrease of thyroid hormones or blocking of the actions of deiodinases may play a role.

Key words: hyperthyroidism, antithyroid drugs, creatine kinase, myalgia

INTRODUCTION

In Taiwan, the principal treatment for hyperthyroidism is antithyroid drug (ATD) therapy with agents including propylthiouracil and methimazole, which usually restores euthyroidism within one to three months[1]. Such treatment, however, may result in significant side effects[2] including rash, urticaria, fever, and arthralgia. Rarely, major side effects also occur, including hepatitis, a Systemic Lupus Erythematosis (SLE)-like syndrome, and of most concern, agranulocytosis.

Several case reports have described myalgia and elevations of serum creatine kinase (CK) in patients with Graves' disease undergoing ATD therapy[3,4]. We describe 2 additional patients with increases in serum CK concentrations during ATD treatment for Graves' disease and discuss a possible mechanism to explain this finding.

CASE REPORTS

Case 1

A 27-year-old man was referred to our institution for evaluation of thyrotoxicosis. He had been healthy in the past but had complained of hand tremors and palpitations for two years. His serum thyroxine (T4) level was 21.6 μg/dL (normal range [NR]: 5.1-12.8 μg/dL) and serum thyrotropin (thyroid stimulating hormone, TSH) was < 0.03 μ U/ml (NR: 0.46-4.7 μ U/ml). Serum anti-thyrotropin receptor antibody was 49% (normal < 15%), as measured using a radio-receptor assay. The 24-hour radioactive iodine uptake test as determined by a ^{131}I thyroid scan was 49% (NR: 10-30%). An ultrasonogram of the neck demonstrated a diffuse, nonhomogeneous echogenicity of both lobes of the thyroid gland. The patient was diagnosed with Graves' disease and treatment was begun with propylthiouracil (PTU, 300 mg/day) and propranolol (30 mg/day). He noticed cramps and myalgia 2 weeks after beginning PTU therapy, at which point the serum T4 level was 6.71 μg/dL, the serum TSH was < 0.03 μU/ml, and the serum CK level was 2130 U/L (NR: 43-272 U/L). He was admitted to the hospital and the PTU was stopped, with a prompt improvement in symptoms. An electromyography examination was normal. The patient then received ^{131}I treatment. As shown in Figure 1, the serum CK gradually normalized after stopping ATD treatment. Furthermore, the TSH remained below the normal range and the free T4 1.91 ng/dl (NR: 0.8-2.0 ng/dl) was in the normal range at the 6-month follow-up. The patient was clinically stable on propranolol (30 mg/day) therapy. There were no comorbidities during the entire treatment course. This patient was lost to follow-up after the 6-month treatment period.

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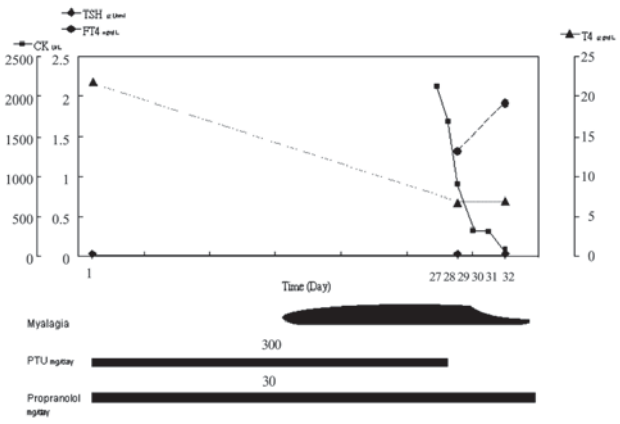

Fig. 1 Clinical course of case 1. Serum concentrations of thyroxine (T4), thyrotropin (TSH), and creatine kinase (CK), and symptoms of myalgia during treatment.

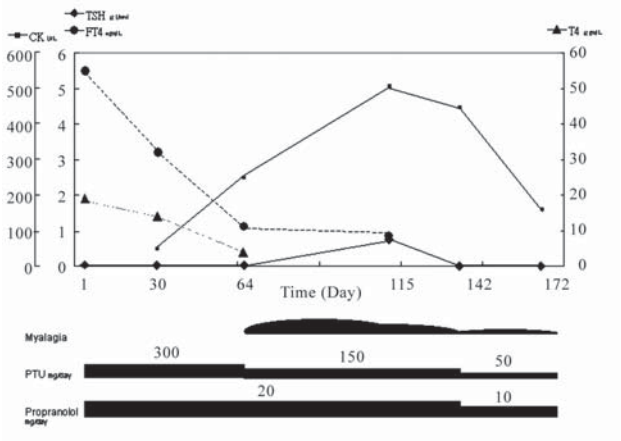

Fig. 2 Clinical course of case 2. Serum concentrations of thyroxine (T4), thyrotropin (TSH), and creatine kinase (CK), and symptoms of myalgia during treatment.

Case 2

A 40-year-old man was diagnosed with Graves' disease based on clinical symptoms of thyrotoxicosis and laboratory findings of a serum T4 level of 19.0 μg/dL and TSH < 0.03 μ U/ml. He was initially prescribed PTU 300 mg/day and propranolol 20mg/day. The patient had been in his usual state of good health until starting treatment, but approximately 2 months later he began to notice myalgia and cramps. Laboratory tests revealed a serum CK level of 249 U/L, a free T4 level of 1.11 ng/dL and a serum TSH < 0.03 μ U/ml, after which his PTU dosage was tapered to 150 mg/day. However, the CK level remained elevated at 504 U/L with a serum-free T4 level of 0.86 ng/dL and TSH of 0.76μU/ml 4 months after starting ATD medication, at which point the patient still had the clinical symptoms of myalgia and cramps, but no more seriously than before. There were no comorbidities during the entire treatment course. The dosages of PTU 150 mg/day and propranolol 20mg/day were tapered to 50 mg/day and 10 mg/day respectively, after which the CK level gradually decreased to 160 U/L about 6 months after ATD treatment, as illustrated in Figure 2. The patient did not follow up at our outpatients department after the 6 months of medical treatment.

DISCUSSION

Although elevation of serum CK concentration is common in patients with hypothyroidism, the exact mechanism for this increase is unknown[5]. Elevation of serum CK is common in patients with overt hypothyroidism when compared to patients with subclinical hypothyroidism[6]. Possible mechanisms for this effect are reduced glycolysis and oxidative phosphorylation, causing lower intracellular ATP concentrations, which then render the sarcolemmal membranes permeable to CK[6]. Another possibility is that hypothyroidism reduces turnover of CK, allowing serum levels to rise[7]. Serum CK is typically either normal or low in hyperthyroidism[8], and is significantly lower in patients with subclinical hyperthyroidism compared with euthyroid and hypothyroid patients[9].

Shergy and Caldwell reported a case of a patient with high CK levels after PTU therapy[10], however, the patient had both hyperthyroidism secondary to Graves' disease and polymyositis, and it is therefore difficult to ascertain whether the CK elevation was a consequence of ATD or related to increasing disease activity of the polymyositis. Suzuki et al. described 4 cases of adult patients with Graves' disease and an abnormal increase in serum CK concentrations during treatment with ATD, and speculated that the rapid decrease in thyroid hormone resulted in a local hypothyroid state within the muscle tissue, which may have contributed to the CK elevations[3]. Recently, Mizuno reported a case of a child with hyperthyroidism who developed an elevation in CK after initiating ATD therapy[4].

Because the serum level of CK increased after the administration of the ATD in both patients described in this report, the levels decreased after withdrawing or tapering the dosage, and neither patient was taking other medications, we suspect that the ATD caused the CK elevations. Several possible mechanisms have been proposed by Suzuki and Mizuno based on their clinical experience to explain the

correlation between ATD and serum CK levels, which include: 1) a direct effect of the ATD on muscle, 2) effects mediated by the immunosuppressive actions of the ATD, 3) inhibition of the production of thyroid hormone resulting in a local hypothyroid state within the tissues, and 4) a potential side effect of the β-blocker[3,4]. In our patients, β-blockers were continued through the course of treatment, therefore, it is not likely that β-blockers contributed to the elevation of CK. An acute decrease in thyroid hormone noted after the ATD was prescribed may, however, account for the correlation.

Common side effects of ATDs include rash, urticaria, and fever (1 to 5% of patients), and the incidence of myalgia is very rare. The side effects often develop within 3 months of starting the ATD, but may occur up to 1 year later. The responses of the 2 patients to the PTU therapy were quite different, especially the dynamic changes of CK levels during and after stopping PTU. In case 1, the CK levels reduced to within the normal range within days after PTU was discontinued, whereas in case 2, the CK level returned to normal more slowly than in case 1. The possible explanation for the difference is that we discontinued PTU in case 1, but continued ATD at a lower dose in case 2. Individual variation in responses to PTU should also be considered.

The most important pathway for T4 metabolism is mono-deiodination of its outer ring (5') to yield the active thyroid hormone, tri-iodothyronine (T3). This reaction is catalyzed by type 1 and type 2 deiodinases (D1 and D2). Another pathway is inner ring deiodination, which is catalyzed primarily by type 3 deiodinase (D3), leading to inactivation of T4 and T3[11]. The expression and activities of the deiodinases differ in between tissues. The liver, kidney, thyroid, and pituitary express high levels of D1, with lesser amounts found in the brain. In contrast, D2 is most abundant in the pituitary, brown adipose tissue, thyroid, heart, and skeletal muscle, while D3 expression occurs primarily in the brain. PTU causes a dose-related inhibition of T3 production, which is most readily seen in thyrotoxic patients in whom T4-to-T3 conversion via the D1 pathway is markedly increased[12]. The deiodinase processes shift towards D2, which is associated with decreasing thyroid hormone in the skeletal muscle. This local hypothyroid status in skeletal muscle may thus result in CK elevation.

There is no definitive rule to manage CK level elevation during or after ATD therapy. When side effects occur, we may initially discontinue the ATD and follow up the clinical condition of the patient, as in the case 1. Alternatively, if the symptoms are mild, we may taper the dosage of PTU as presented for case 2. Side effects of methimazole are dose related, whereas those of PTU are less clearly related to dose. Thus, we should consider another therapeutic plan to treat thyrotoxicosis, such as ^{131}I ablation or surgery, if a patient develops severe myalgia.

There are no obvious risk factors predisposing patients with Graves' disease to elevation of CK levels after ATD therapy. One possible factor is rapid normalizing of hyperthyroidism to euthyroidism or subclinical hyperthyroidism within 1 to 2 months. Therefore, the initial PTU dosage should be modified according to the laboratory findings and clinical symptoms.

In conclusion, we observed myalgia, muscle cramps, and an elevation of serum CK levels after treatment with an ATD for Graves' disease. The mechanism for this correlation is not clear. Nevertheless, the rapid decrease of thyroid hormone in tissues could temporarily cause a hypothyroid state. Additionally, PTU blocks D1 deiodinases, which may have caused D2 deiodinases to dominate, increasing the leakage of CK from skeletal muscles. Clinicians should be aware of the rare potential for elevations in serum CK levels when initiating treatment for Graves' disease with an ATD.

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