transduction of mast cells leading to cytokine production and degranulation. IL-6 production and degranulation were inhibited in BMMCs derived from PKCβ-deficient mice (37). JNK activation and the transactivation of *IL-2* and *TNF-α* promoter were suppressed by overexpression of kinase-dead PKCβ in BMMCs (27). Furthermore, it has been reported that PKCβII regulates Akt activity by directly phosphorylating Ser^{473}, which regulates the cytokine production from mast cells (28, 38). Hence, the down-regulation of PKCβ seems to be a major factor in the inhibition of mast cell activation by the repression of GATA activity.

In contrast to degranulation and cytokine production, it has been reported that the deficiency of PKCβ in mast cells did not affect their rate of proliferation and apoptosis (37). This fact indicates the contribution of mechanisms other than the down-regulation of PKCβ to the survival of mast cells. In this study, the decreased expression of apoptosis-related genes such as *Bcl-x_L* and *Bcl-A1*, and decreased histone acetylation in the *Bcl-x_L* gene were observed in GATA-repressed mast cells (Table I). Probably the expression of numerous genes is down-regulated through modification of histone acetylation after repression of GATA activity because this function of GATA has a broad activity that can influence hemopoiesis (39). Taken together, we have demonstrated that the repression of GATA activity suppressed various activities of mast cells. Our report may indicate an important clue to treat mast cell-mediated diseases.

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Disclosures

The authors have no financial conflict of interest.

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Short communication

Myopathy in thiamine deficiency: Analysis of a case

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Abstract

Background: Tenderness in the limb muscles has been reported anecdotally in patients with beriberi neuropathy, but clinical effects of thiamine deficiency on skeletal muscle have received little attention.
Objective: To describe a patient with thiamine deficiency who manifested myopathic symptoms and responded well to thiamine supplementation.
Patient: A 26-year-old woman with neuropathy and heart failure associated with thiamine deficiency also complained of myalgia and weakness, most troublesome in the proximal portions of the limbs.
Results: Serum creatine kinase, myoglobin, and aldolase concentrations were abnormally elevated. Magnetic resonance imaging of lower limb muscles demonstrated areas of high signal intensity in T2-weighted images and showed Gd-DTPA enhancement. A biopsy specimen from the quadriceps muscle showed myopathic changes without neurogenic changes. Abnormalities improved well with thiamine administration.
Conclusion: Myopathy may occur in patients with thiamine deficiency.

Keywords: Thiamine deficiency; Beriberi; Neuropathy; Myopathy; Muscle biopsy

1. Introduction

Thiamine deficiency occurs in various clinical contexts including dietary imbalance, chronic alcoholism, prolonged parenteral nutrition, and postgastrectomy states [1–5]. Deficiency is known to affect the heart (i.e. wet beriberi), peripheral nervous system (i.e. dry beriberi), and central nervous system (i.e. Wernicke–Korsakoff syndrome) with wide variation in site and severity of involvement between individual patients [3,4]. In addition to involvement of these various organs, pain in limb muscles showing exacerbation with palpation has been reported anecdotally in association with beriberi neuropathy [1]. Although efficient glucose metabolism, which requires thiamine, is an important source of ATP needed for skeletal muscle contraction, little attention has been given to clinical effects of thiamine deficiency on skeletal muscles.

We report a patient with thiamine deficiency who manifested myopathic symptoms in addition to neuropathy and heart failure, and responded well to thiamine supplementation. We believe that this is the first account to include full laboratory evaluation of skeletal muscle involvement in thiamine deficiency.

2. Case report

Five years before admission to the hospital, a 26-year-old woman first noted muscle pain in both thighs when she walked for a long distance. Two years later she became aware of edema and weakness in the legs. She experienced difficulty in standing from a squatting position. Numbness appeared in the toes and gradually spread throughout both feet. Orthopnea developed 4 months prior to admission. When admitted she could barely walk without assistance.

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The patient disliked eating meat or vegetables, preferring milled white rice with no side dishes. She took these meals at very irregular intervals. She drank coffee many times a day, consuming a considerable amount of sugar with it. She had no intake of alcohol. She had maintained these dietary patterns for at least 6 years. She did not have a family history of myopathy or thiamine deficiency. At the time of admission her body weight was 59 kg while height was 155 cm. Pitting edema was conspicuous throughout the legs. Myalgia, exacerbated by palpation, was present in proximal extremity muscles. Neurologic examination disclosed no impairment of consciousness. Cranial nerves were normal. Mild weakness was present in the neck flexor muscles; weakness was moderate to severe in the lower extremities. Lower extremity muscle weakness was more predominant proximally than distally. No muscle weakness was apparent in the upper extremities. Sensory loss affected in all modalities in a glove-stocking pattern distally from the wrist and from the middle of the thigh. Deep tendon reflexes generally were hypoactive, with greater reduction in the lower limbs.

Serum creatine kinase (CK) was elevated at 499 IU (normal, 45 to 245). Myoglobin and aldolase also were elevated, to 254 ng/ml (normal, <60) and 7.9 IU (normal, 2.2 to 7.3) respectively. Aspartate aminotransferase and lactate dehydrogenase were 43 IU (normal, 45 to 245) and 376 IU (normal, 100 to 250). Total thiamine concentration in whole blood was 16 ng/ml (normal, 20 to 50). Lactate was 24 mg/dl (normal, 6 to 20), while pyruvate was 1.3 (g/dl (normal, 0.3 to 1.0). Concentrations of vitamin B2, vitamin B6, vitamin B12, folate, vitamin D, and vitamin E all were normal. Total serum protein and albumin concentrations were not decreased. C-reactive protein and erythrocyte sedimentation rate were normal. Results of hormonal assays including those related to the hypophysis and thyroid gland were normal, except for a slightly elevated serum prolactin concentration. Chest radiography demonstrated large bilateral pleural effusions and moderate cardiomegaly with pulmonary congestion.

Findings of nerve conduction studies were those of axonal neuropathy, most pronounced in the lower limbs. Motor conduction velocities in the median and tibial nerves were normal (57 and 50 m/s, respectively). Amplitudes of compound muscle action potentials were preserved in the median nerve (24 mV) but reduced in the tibial nerve (0.9 mV). Sensory conduction velocities were mildly reduced in the median and sural nerves (44 and 37 m/s, respectively). Sensory nerve action potentials were 10 μV in the median nerve and 3 μV in the sural nerves. A sural nerve biopsy specimen showed axonal degeneration on cross section as well as in a teased-fiber preparation. Severe loss of large myelinated fibers and mild to moderate loss of small myelinated fibers and unmyelinated fibers were observed. Profound edema was evident in the subperineurial space. T2-weighted magnetic resonance imaging (MRI) in the thigh demonstrated areas of high signal intensity especially in the vastus lateralis and biceps femoris muscles (Fig. 1A). In the leg, similar findings were seen in the tibialis anterior and soleus muscles. T1-weighted images after Gd-DTPA administration showed mild enhancement of these muscles (Fig. 1C). A biopsy specimen from the quadriceps muscle showed variation in fiber diameter. In hematoxylin and eosin-stained sections the atrophic muscle fibers tended to show rounded cross-sectional profiles; small angulated fibers were not observed. Fiber with internal nuclei was not increased. Obvious necrotic fiber was not observed, but occasional regenerating (basophilic or multinucleated) fibers were present (Fig. 2A and B). No inflammatory infiltration was found in any section. In ATPase-stained sections (preincubated at pH 9.8) the ratio of type I to type II fibers was approximately 1:2, indicating no predominance in fiber type (Fig. 2C). Fiber-type grouping also was not observed. Variation in diameter was observed in both type I and type II fibers. Ragged-red fiber was not observed. By electron microscopy, number of mitochondria was slightly increased in subsarcolemma and clustering of mitochondria was seen frequently in perinuclear and perivascular areas (Fig. 2D). No alteration of mitochondrial or of myofibrillary structure was apparent. Paracrystalline inclusion was not present.

The patient was given a 75-mg daily oral dose of fursultiamine, a disulfide derivative of thiamine, beginning at the time of admission. Cardiomegaly, pleural effusions, and edema in the legs decreased dramatically within a few days after beginning thiamine administration. Neurologic symptoms and CK level also improved gradually. Improvement of muscle strength was evident at 1 week, especially proximally. MRI repeated 1 month later showed neither high signal intensity in T2-weighted images nor abnormal gadolinium enhancement in the muscles of the lower limbs (Fig. 1B and D). Myalgia subsided in 2 months. Substantial recovery of muscle strength and normalization of CK level was achieved 3 months later. Recovery of sensation was less complete than motor recovery.

3. Discussion

Although myalgia is frequently observed in patients with thiamine deficiency [1,3,4], its precise mechanism has not yet been clarified. Thiamine pyrophosphate, the physiologically active form of thiamine, functions in carbohydrate metabolism as a coenzyme in decarboxylation of α-ketoacids such as pyruvate. Thiamine deficiency decreases generation of ATP, by disrupting the major metabolic pathways for carbohydrates, as thiamine is needed for entry of pyruvate into the Krebs cycle in the mitochondrial matrix. Because muscle consumes large amounts of ATP when it contracts, reduction of ATP may cause muscle dysfunction or injury, as is most widely appreciated from the effect of thiamine deficiency on cardiac muscle (i.e. wet beriberi). Further, an animal study demonstrated that thiamine deficiency causes atrophy and necrosis of skeletal muscle fibers [6].

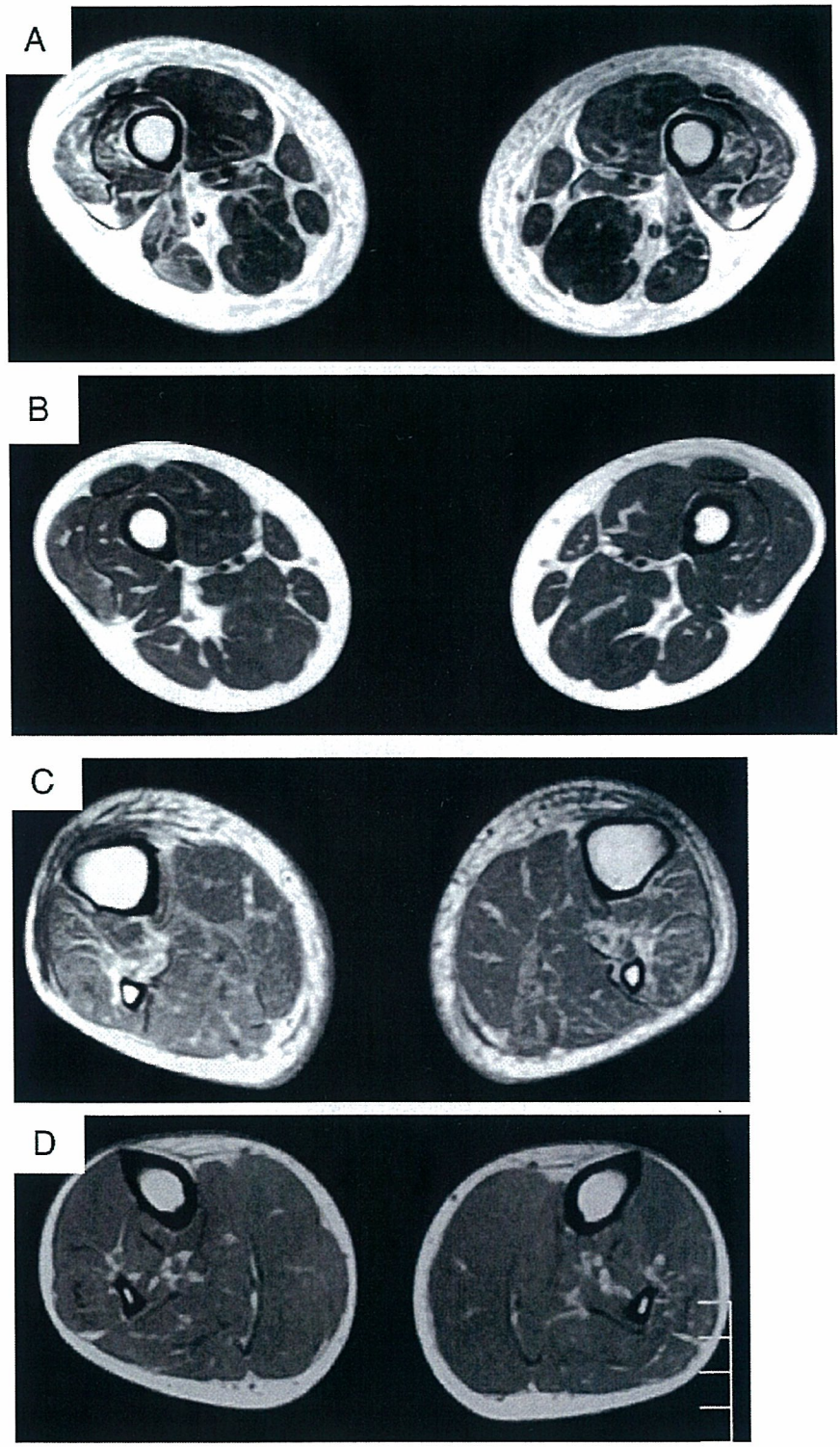

Fig. 1. Magnetic resonance imaging (MRI) of lower limb muscles. Before thiamine administration, a T2-weighted image of the middle thigh showed areas of high signal intensity especially in the vastus lateralis and biceps femoris muscles (A). One month later, areas of high signal intensity had disappeared (B). Gd-DTPA-enhanced image of the middle leg before thiamine administration, showing mild enhancement in the tibialis anterior and soleus muscles (C). One month later, no abnormal gadolinium enhancement was seen in these muscles (D).

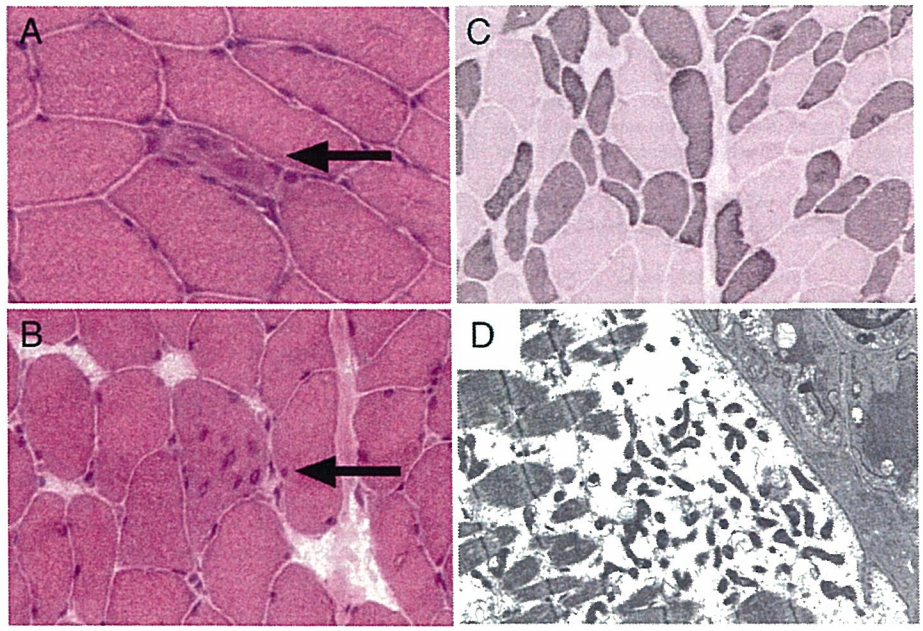

Fig. 2. Findings in a biopsy specimen from the quadriceps muscle. Specimens were stained with hematoxylin and eosin (A, B), ATPase preincubated at pH 9.8 (C), and uranyl acetate plus lead citrate (D). By light microscopy, basophilic fibers (A), and multinucleated fibers (B) occasionally were present, suggesting gradual muscle fiber loss and regeneration. The ratio of type I to type II fibers was approximately 1:2, indicating no predominance in fiber type or neurogenic change (C). By electron microscopy, a cluster of mitochondria was seen in perivascular area (D).

In addition to reduced ATP production, thiamine deficiency may affect skeletal muscle through accumulation of pyruvate not consumed in the Krebs cycle. Because pyruvate is converted to lactate in the liver by lactate dehydrogenase, both pyruvate and lactate increase in the blood during a thiamine-deficient state. Elevation of serum lactate may be related to myalgia in beriberi, because accumulation of lactate in skeletal muscle has been regarded classically as the most important cause of muscle fatigue. However, recent work has challenged this view; lactate may exert a positive effect on muscle contractility [7].

Mitochondrial myopathies may cause similar features to our case. They include myopathy, cardiomyopathy, neuropathy, and lactic acidosis [8,9]. A family with mitochondrial myopathy with mitochondrial DNA mutation and familial thiamine deficiency that responded to thiamine supplementation has been reported [10], suggesting the close relationship between mitochondrial function and thiamine utilization. Although number of mitochondria seemed to be slightly increased in subsarcolemma in our case, findings seen in typical mitochondrial myopathies such as ragged-red fibers or alteration of mitochondrial structure were not observed. Thus, the primary cause of clinical manifestations in our case is likely to be thiamine deficiency, but not mitochondrial abnormality. However, genetic factors, including those related to mitochondrial function, may determine the susceptibility of skeletal muscle to thiamine deficiency as suggested in Wernicke–Korsakoff syndrome and thiamine-responsive megaloblastic anemia [11–14]. Indeed, not all patients with thiamine deficiency report myalgia [3,4].

Myopathy associated with chronic alcoholism has been reported frequently [15,16]. In addition to direct effects of ethanol on skeletal muscle, nutritional deficiency has been implicated [16]. Anorexia nervosa also may induce myopathy [17]. A previous survey of nervous system complications following gastric surgery noted myopathy in 6 of 34 cases [18]. In these previous studies, myopathy probably was caused partly by nutritional deficiency, but the specific contribution of thiamine deficiency was not a focus. In myopathies associated with chronic alcoholism and anorexia nervosa, atrophy of type II fibers was reported [15,17]. On the other hand, our case was not characterized by fiber-type selectivity. Considering the MRI finding of intense T2 hyperintensities and the finding of Gd-DTPA enhancement, increased vascular permeability causing edema in skeletal muscle may have contributed significantly to myopathy in our case. Further investigation is still needed to clarify the effect of thiamine deficiency on skeletal muscle.

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