Hypokalemic Myopathy Associated with Primary Aldosteronism and Glycyrrhizine-Induced Pseudoaldosteronism

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Abstract

Enzymatic and histological features of muscular disorders associated with primary aldosteronism and glycyrrhizine-induced pseudoaldosteronism were studied. Among 10 patients with primary aldosteronism and 3 patients with pseudoaldosteronism, 5 patients were admitted to our hospital because of muscular weakness. The serum potassium (K) level was 1.86±0.21 mEq/l in a myopathy group on admission, a value significantly less than that of the 2.74±0.10 mEq/l in a non-myopathy group (p<0.01). Serum creatine phosphokinase (CPK), glutamate-oxaloacetate transaminase (GOT), and lactate dehydrogenase (LDH) were increased in the myopathy group compared to the non-myopathy group; serum CPK was 1412.6±902.6 vs. 22.8-15.0 mU/ml, serum GOT was 186.4±75.3 vs. 24.2±5.4 mU/ml (p<0.05), and serum LDH was 1133.4±377.3 vs. 387.6±42.5 mU/ml (p<0.05) in the groups with and without myopathy. Analysis of CPK isozymes revealed that the MM type exceeded 95%. The elevated serum CPK, GOT and LDH rapidly decreased to the normal range and muscular strength completely improved within 6 to 13 days after hospitalization, when the serum K level remained below than normal. Light microscopic finding of damaged muscle showed the diffuse necrosis and vacuolization of muscle fibers. Electron microscopic study clearly demonstrated complete dissolution of myofilaments with disappearance of sarcoplasmic reticulum and T-tubules in the necrotic muscle fibers. These results indicate that muscular lesions may occur in primary aldosteronism and pseudoaldosteronism when the serum K level is decreased to below 2.0 mEq/l. This myopathy is not periodic paralysis but hypokalemic myopathy. The mechanism by which K deficiency causes muscular damage remains unknown.

Muscular weakness chiefly in the proximal limbs is one of chief complaints in patients with primary aldosteronism (Conn et al., 1964). In 1972 Sambrook, Heron, and Aber (1972) initially showed the light microscopic findings of muscular fiber necrosis in primary aldosteronism. We further studied the electron microscopic findings of damaged muscle in one patient with primary aldosteronism (Atsumi et al., 1979). Licorice-induced hypokalemia also causes muscular weakness (Conn et al., 1968). Light and electron microscopic findings of muscle fiber necrosis were reported by several investigators (Gross...
et al., 1966; Mohamed et al., 1966). An acute myopathy is suggested to relate to hypokalemia, showing this muscular disorder to be "hypokalemic myopathy." Gastrointestinal potassium (K) loss, administration of diuretics and chronic alcoholism can also induce hypokalemic myopathy (Van Horn et al., 1970; Uchiyama et al., 1977; Martin et al., 1971). In hypokalemic myopathy there is a major histological finding of muscular fiber necrosis, which accompanies the elevation of serum enzymes derived from the damaged muscles. Such clinical and histological findings seem quite similar to those of myopathy with primary aldosteronism (Sambrook et al., 1972; Atsumi et al., 1979). Except for the above two, however, previous reports (Conn et al., 1964; Liddle, 1981; Bantista et al., 1979) described muscular disorders of primary aldosteronism as periodic paralysis or episodic paralysis of the extremities, with little histological examination. Since we reported our first case, we have had 3 patients with myopathy associated with primary aldosteronism and 2 patients with glycyrrhizine-induced hypokalemic myopathy. The present study was undertaken to determine the enzymatic and histological features of hypokalemic myopathy due to primary aldosteronism or glycyrrhizine-induced pseudoaldosteronism. Also, we describe the difference between enzymatic and histological findings in hypokalemic myopathy and periodic paralysis, and show that the muscle damage related to primary aldosteronism is in concert with hypokalemic myopathy.

Materials and Methods

Subjects

Ten patients with primary aldosteronism (5 males and 5 females, 26 to 55 years old) and 3 patients with glycyrrhizine-induced pseudoaldosteronism (one male and 2 females, 54 to 79 years old) have been admitted to Jichi Medical School Hospital since 1974. Five of them had complained chiefly of muscular weakness on admission. Muscular weakness was distributed over proximal extremities (in all 5 patients), distal extremities (patients HS, KK, and KA) and neck (patients HS and KA), but respiratory muscles were not involved. Deep tendon reflexes were diminished in all 5 patients. These five cases comprised the myopathy group. Sensory systems were normal. The other 8 patients were admitted because of hypertension or hypokalemia. Two patients of this group had a history of muscular weakness in their extremities. These eight cases comprised the non-myopathy group. Also, the drugs administered prior to admission were revaluated. Serum electrolytes, sodium (Na) and potassium (K), blood gas analysis and serum enzymes such as creatine phosphokinase (CPK), glutamate-oxaloacetate transaminase (GOT) and lactate dehydrogenase (LDH) were measured. Blood samples were collected from the patients kept in a supine position to measure the plasma renin activity (PRA) and plasma aldosterone concentration. PRA and plasma aldosterone were measured with radioimmunoassay kits (PRA radioimmunoassay kit, Midori-Juji, Tokyo, Japan; and Aldosterone radioimmunoassy kit, Dainabott Lab., Tokyo, Japan). These parameters were measured frequently while they were in hospital to detect changes in serum electrolytes and enzymes associated with the alleviation of muscular weakness. Also, during an acute episode of muscular weakness, the electrocardiogram (ECG) and electromyogram (EMG) were examined. Muscular biopsies were taken from 3 patients (HS, SO, and KK) during an acute phase of muscular disorder. Adrenal adenomas were resected in all the patients, with primary aldosteronism demonstrated in this paper, and were histologically confirmed as being benign adrenal adenoma (aldosteronoma).

Histological studies

Muscle biopsies were performed in the femoral quadriceps muscle during a period of muscular weakness (patients HS and SO) and on the 12th days after admission (patient KK). The fixed and frozen specimens were prepared for histological and histochemical studies. For the electron microscopic study, the muscle specimens were fixed in 2% glutaraldehyde for 2 hrs and then kept in 1% osmium tetroxide. The tissues were dehydrated in a series of ethanol solution and
embedded in a mixture of Epon and Araldite. Sections were cut, stained with lead citrate and uranyl acetate, and examined with a JEM 100B Electron Microscope.

Statistics
Serum K, CPK, GOT and LDH levels in the two groups were compared by Student's t-test. A P value less than 0.05 was considered significant.

Results
Table 1 summarizes the clinical data for 13 patients. All 13 patients were hypertensive. Serum K levels were below the normal range in all the patients. Serum K levels of 1.86±0.21 mEq/l (mean±SEM) in a group with myopathy were significantly lower than those of 2.74±0.10 mEq/l of a group without myopathy (p<0.01) (Fig. 1). All the patients showed metabolic alkalosis. Reduced PRA and elevated concentrations of plasma aldosterone strongly suggested primary aldosteronism. This was further confirmed with an adrenal scintigram, adrenal venogram, and adrenal venous aldosterone concentrations (data not shown). Low PRA was also found in all 3 patients with glycyrhizine-induced pseudoaldosteronism. One patient had a plasma aldosterone normal level and the other 2 patients had reduced levels of plasma aldosterone in pseudoaldosteronism. It should be noted that thiazides were administered in all 5 patients with myopathy before admission.

Figures 2 to 4 show serum levels of CPK, GOT and LDH on admission. The group with myopathy had marked elevations of serum CPK, GOT and LDH, but this was not found in the group without myo-

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<th>Table 1. Clinical Data for 13 Patients with Primary or Pseudo-Aldosteronism.</th>
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<td>Primary Aldosteronism</td>
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<td>(a) Myopathy group</td>
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Fig. 1. Serum potassium (K) levels in two groups of patients with and without myopathy.

Fig. 2. Serum CPK levels in two groups of patients with and without myopathy.

Fig. 3. Serum GOT levels in two groups of patients with and without myopathy.

Myopathy except for two patients (MN and KA) whose liver dysfunction was complicated by mild elevation of serum GOT, GPT, and LDH. A liver biopsy of patient MN showed early liver cirrhosis. Indocyanine green excretion was 21% in patient KA (the normal level is below 10%). The GOT value in the myopathy group was 184.6 ± 75.3 mU/ml, a value significantly greater than the 24.2 ± 5.4 mU/ml in the non-myopathy group (p < 0.05). Similarly, the LDH value of 1133.4 ± 377.3 mU/ml in the myopathy group was significantly greater than the 387.6 ± 42.5 mU/ml in the non-myopathy group (p < 0.05). Analysis of CPK isozymes demonstrated more than 95% of the MM type in all the patients with myopathy, thus indicating that the elevation of serum CPK levels was due to damaged skeletal muscles. Myoglobinuria was detected in 3 patients on admission.

Figure 5 shows the clinical course of
Fig. 4. Serum LDH levels in two groups of patients with and without myopathy.

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Fig. 4. Serum LDH levels in two groups of patients with and without myopathy.

serum K and CPK in patients with myopathy. The elevated serum CPK level rapidly fell to the normal range within 6 to 13 days after hospitalization. These changes in serum CPK were quite parallel to the improvement in muscular strength. Serum CPK returned to normal before the serum K level increased to the normal range. Patients HS, SO, and KK were followed up without replacement of KCl, and serum K levels thus remained below the normal range. KCl was administered intravenously to two other patients (MN and KA) with pseudoaldosteronism to raise serum K level rapidly. Even in the latter two patients serum CPK and muscular strength recovered prior to the normalization of the serum K level. Similar results were obtained with the clinical course of serum GOT and LDH.

ECG showed ST depression, flat or inverted T wave and U wave, thus revealing the influence of hypokalemia on heart muscle. Myogenic changes also were indicated by the EMG of the deltoid, quadriceps and hamstring muscles, as the low amplitude of the neuromuscular unit was found.

Microscopic study demonstrated the diffuse necrosis and vacuolization of muscle fibers, infiltration of phagocytes and basophilic regenerating fibers in an acute stage of muscular weakness (Fig. 6A). Histological reactions revealed both type 1 and 2 muscular fibers were damaged. Electron microscopic findings of necrotic muscle fibers were complete dissolution of myofilaments with disappearance of sarcoplasmic reticulum and T-tubules. Degenerated vacuoles, membranous bodies and lipid granules were also found in the dissolved myofilaments, but, in contrast, mitochondria kept its structure in the dissolved myofilaments (Fig. 6B). Ultrastructures of non-necrotic muscle fibers demonstrated membrane-bound vacuoles (Fig. 6C), and dilatation of sarcoplasmic reticulum and widening of the T-tubules (Fig. 6D). However, only vacuolization was found in the quadriceps muscle of patient KK, on whom the biopsy was performed during the phase of recovery from muscular weakness.

Discussion

Muscular damage was demonstrable in 5 patients with primary aldosteronism and pseudoaldosteronism, and it is closely related to hypokalemia. This was confirmed by both enzymatic and histological examinations. The histological studies clearly show the necrosis of muscle fibers accompanied with vacuolization of muscle fibers, dilatation of sarcoplasmic reticulum and widening of the T-tubules. The histological findings of one of the 3 patients with primary aldosteronism has already been reported elsewhere (Atsumi...
We conclude that the change in serum enzymes of CPK, GOT and LDH were associated with the muscular necrosis. All three enzymes were increased in serum, due probably to leakage from the damaged skeletal muscles. Analysis of CPK isozyme, predominantly of MM type, ruled out the possibility that the elevated serum CPK level was derived from heart muscle, although typical ST depression and U wave were found in ECG. We could not differentiate between the characteristics of muscular damage in primary aldosteronism and pseudo-aldosteronism. Therefore, both of them were combined to form a group with myopathy. This was called “hypokalemic myopathy.” Previous authors (Conn et al., 1964; Liddle, 1981; Bantista et al., 1979) have not accurately evaluated the muscular disorders of primary aldosteronism, since they have described periodic paralysis or episodic paralysis of the extremities. The present study clearly ruled out periodic paralysis as the myopathy of primary aldosteronism, because periodic paralysis is not associated with the necrosis of muscle fibers or minor changes in serum enzymes. Periodic paralysis results only vacuolization in muscle fibers (MacDonald et al., 1969; Ionasescu et al., 1974), but the necrosis of muscle fibers is the major change in hypokalemic myopathy (Atsumi et al., 1979; Gallai, 1977; Hashimoto et al., 1980).
Fig. 6. (A) Hematoxylin-eosin stain of femoral quadriceps muscle of patient HS. Frozen section (×320). Diffuse muscle fiber necrosis and phagocytosis are found. Vacuoles are also found in non-necrotic muscle fibers.

(B) Ultrastructure of necrotic muscle fibers in femoral quadriceps muscle of patient HS (×5,400). There is dissolution of myofilaments with degenerated vacuoles, membranous bodies, and lipid granules. Mitochondria, however, retains its structure in the dissolved myofilaments. Sarcoplasmic reticulum and T-tubules have totally disappeared.

(C) and (D) Ultrastructure of non-necrotic muscle fibers of femoral quadriceps muscle. (C) shows various membrane-bound vacuoles (×7,500) and (D) shows dilatation of sarcoplasmic reticulum and widening of T-tubules (×13,500).

Although hypokalemia was present in both groups with and without myopathy, there was a significant difference between the serum K levels in the two groups. Myopathy may occur when the serum K level drops to below 2.0 mEq/l, except for patient KK who had a different clinical course from the other 4 patients with myopathy. Patient KK had a history of 4 episodes of muscular weakness during the last half a year. Such muscular disorders had occurred though serum K levels ranged from 2.4 to 2.8 mEq/l. As shown in Fig. 5, elevated serum CPK rapidly normalized within 6 to 13 days after the hospitalization but serum K level remained below the normal range. Normalization of serum K level, thus, may not be necessary to regenerate the damaged muscles, and the muscular damage may occur transiently. These findings
suggest an additional, unknown factor may be involved in the onset of muscular damage when serum K level is reduced to less than 2.0 mEq/l. We don't know whether elevated aldosterone or mineralocorticoid-like substance, glycyrrhetinic acid, might directly affect the skeletal muscle to cause myolysis (Patterson et al., 1983). Knochel and Schlein (1972) suggested that ischemia may be the mechanism of rhabdomyolysis with exercise in K depletion.

The drugs administered to the patients on admission are listed in Table 1. All 5 patients with myopathy were treated for their hypertension with thiazides. Thiazides are agents known to increase renal K excretion and lower the serum K level. It is probable that thiazides may have lowered the serum K level further in these patients to cause muscular damage.

As described above, severe hypokalemia results in muscle destruction. Some cases of hypokalemia-induced muscle injury leading to acute renal failure have been reported in literature (Knochel, 1976; Nadel et al., 1979). In our study 3 patients had a transient myoglobinuria, but renal function was not disturbed during their clinical courses as there was no finding of the elevation of serum urea nitrogen (BUN) or creatinine. Renal insufficiency following hypokalemic myopathy may be dependent on the severity of muscle necrosis the same as other causes of myopathy (Knochel, 1976; Nadel et al., 1979).

To sum up, muscle weakness occurs not infrequently in patients with primary aldosteronism and glycyrrhizine-induced pseudo-aldosteronism when the serum K level drops to below 2.0 mEq/l. That muscle fiber
necrosis is a feature of this myopathy, that is demonstrated by both enzymatic and histological examinations. These results indicate that hypokalemic myopathy is associated with muscle damage in primary and pseudoaldosteronism. The mechanisms by which K deficiency causes muscle disease remain unknown.

References


