The First Report of a Case with Acute Myocardial Infarction Showing Familial Deficiency of Creatine Kinase

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A 46-year-old male patient was diagnosed as suffering from acute myocardial infarction, but his serum creatine kinase (CK) level was extremely low and no CK isozymes were detected in the serum. The total CK activities in the skeletal muscle amounted to only 2% of that of the control. Electrophoresis of the CK isozymes in the skeletal muscle showed that CK-MM was absent but the CK-BB and abnormal isozyme bands were present. There was no evidence of myocardial ischemia, although the exercise treadmill test revealed ST segment depression in the chest leads. One of the patient's sisters had an extremely low serum CK level suggesting inheritance of this abnormality. This is the first report of a case showing familial deficiency of CK.

Key words: CK isozymes, adenylate kinase, inheritance

Introduction

CK plays an important role in supplying ATP for muscle contraction, and the serum CK level is known to rise in patients with myocardial and skeletal muscular disorders. Here we report a living patient showing an extremely low serum CK level during an acute phase of myocardial infarction. The patient displayed no apparent clinical symptoms throughout most of his life. Oita et al have reported a patient with deficiency of the CK-MM fraction who had died of acute myocardial infarction (1). In succeeding studies they found a deficiency of the CK-M subunit based on immunological examination (2). We performed biochemical examinations associated with CK on the patient's skeletal muscle and discovered an abnormal deficiency, which may have been inherited.

Case Report

A 46-year-old man was admitted to another hospital on May 10, 1989, complaining of chest pain. The patient's previous medical history had nothing notable. However, his father and his elder brother had died suddenly at the ages of 60 and 56, respectively. Physical examination on admission revealed a blood pressure of 170/110 mmHg, a regular pulse of 78 beats/min, and a temperature of 37°C. Peripheral pulsation at the femoral artery, popliteal, dorsalis pedis and posterior tibial artery on the left side was absent. The electrocardiogram (ECG) on admission revealed normal sinus rhythm with high voltage (SV<sub>1</sub> + RV<sub>5</sub> = 3.8 mV) and ST segment depression by 0.1 mV in leads V<sub>5</sub> and V<sub>6</sub>. The next day the ECG revealed abnormal Q waves in leads III and aVF and inverted T waves in leads II, III and aVF (Fig. 1). Laboratory data on admission were as follows: white blood cell count, 14,700/mm<sup>3</sup>; erythrocyte sedimentation rate, 45 mm/h; aspartate aminotransferase (GOT), 20 IU/l (normal: 8 - 40); alanine aminotransferase (GPT), 5 IU/l (normal: 5 - 35); lactate dehydrogenase (LDH) 399 IU/l (normal: 50 - 400). LDH isozymes were as follows: LDH<sub>1</sub>, 51% (62 - 72); LDH<sub>2</sub>, 31% (1.9 - 3.9); LDH<sub>3</sub>, 9.2% (6.0 - 11); LDH<sub>4</sub>, 2.8% (6.0 - 11); LDH<sub>5</sub>, 5.5% (9.1 - 18); CK, 2 IU/l (normal: 40 - 110 IU/l) and total cholesterol 273 mg/dl. CK isozymes were not detected in the patient's serum because of the extremely low serum CK level. The change in the levels of serum enzymes, GOT and LDH, revealed a typical course of myocardial infarction in the acute phase, but the serum CK level remained low (Fig. 2). Two-dimensional echocardiography revealed marked hypokinesis of the inferior left ventricular wall. Although there was no elevation of the serum CK level, the patient was diagnosed as suffering from acute myocardial infarction and was admitted to Hyogo College of Medicine Hospital on June 23,
on admission  
next day

Fig. 1. Left: ECG on admission showing high voltage ($SV_1 + RV_5 = 3.8 \text{mV}$) and ST segment depression in leads $V_4$ and $V_6$. Right: ECG on the second day of admission showing a Q waves in leads III and $aVF$ and inverted T waves in leads II, III and $aVp$.

Fig. 2. Time course of various enzymes in the serum following the onset of myocardial infarction. WBC and enzymes except for CK (arrow) showed a typical time course of acute myocardial infarction.

Fig. 3. Thallium-201 myocardial scintigraphy showing hypoperfusion in the inferior wall (arrows).

Fig. 4. Right coronary arteriogram showing complete occlusion at segment 2 (arrow).

1989 for evaluation of the cardiovascular system and further examination of the abnormality of the CK level. Thallium-201 myocardial scintigraphy showed severe hypoperfusion of the inferior wall (Fig. 3). On cardiac catheterization, a left ventriculogram revealed hypokinesis of the inferior wall. Coronary angiogram showed complete occlusion in the right coronary artery (Fig. 4), 75% stenosis in the left anterior descending artery (segment 7) and 90% stenosis in the first diagonal branch (segment 9) (Fig. 5). Abdominal aortogram showed complete occlusion in the left common iliac artery. Electrocardiographic findings of the exercise treadmill test at 4 Mets revealed horizontal ST segment depression (0.3 ~ 0.5mV) in leads $V_3$ through $V_6$, which suggested myocardial ischemia. Therefore the patient was subjected to percutaneous transluminal angioplasty (PTCA) to the lesion of segment 7 and segment 9. The result was satisfactory and both lesions were adequately dilated, but ST segment depression on ECG of exercise treadmill test remained (Fig. 6). Thallium-201 stress myocardial scintigraphy after PTCA did not show hypoperfusion during stress in the anterior wall (Fig. 7). The patient was diagnosed as having arteriosclerosis obliterance of the left iliac artery by angiography as mentioned above and was suffering from intermittent claudication. He underwent an ilio-iliac bypass operation on September 14, 1989.

**Evaluation of myocardial metabolism by loading of atrial pacing**

To confirm whether ST depression on ECG during
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Fig. 5. Left coronary arteriogram showing 75% stenosis in the left anterior descending artery (A) and 90% stenosis in the first diagonal branch (B) (arrows).

AT REST        DURING EXERCISE
BEFORE PTCA    AFTER PTCA

Fig. 6. Electrocardiogram of exercise treadmill test performed before and after PTCA showing horizontal ST segment depression in leads V3 to V6.

Exercise could be attributed to the insufficient oxygen supply to the tissue, we determined the myocardial lactate extraction ratio (MLER) during atrial pacing which was begun at the rate of 100/min and increased by 10 beats/min every minute. These procedures have been described elsewhere (3). At the rate of 140/min, horizontal ST segment depression of 0.5 mV in leads V3 through V6 was observed, but lactate production was not observed (MLER decreased from 56% to 25% after pacing). Thus this examination did not indicate the occurrence of myocardial ischemia.

Determination of total CK activity and analysis of CK isozyme in the skeletal muscle

A sample was obtained from the quadriceps muscle during the ilio-iliac bypass operation, as we had obtained informed consent for the biochemical examination of skeletal muscle from the patient. A control sample was obtained from a man who had died of acute myocardial infarction at the age of 58. The skeletal muscle was homogenized with 10% phosphate-buffered saline (PBS), pH 7.4, and the supernatant obtained following centrifugation at 12,000 g for 30 minutes was used for the examination. Total CK activity was determined using a CK assay kit, CK-NAC (Boehringer-Mannheim, Yamanouchi). CK isozyme was separated by electrophoresis at 180 volts for 30 minutes on TAITAN III Lipo plate (Helena Laboratories, Beaumont, Texas, USA) with 0.067 M Tris-barbital buffer, pH 8.6. To estimate the molecular size of the band on electrophoresis, gel filtration was also performed on a Sephadex G-200 column (Pharmacia Fine Chemicals, Uppsala, Sweden), which was eluted with phosphate buffer (0.006 M, pH 7.2) at a flow rate of 360 µl/min. The relative molecular size of the CK isozyme in the patient’s sample was estimated by comparison with standard proteins.

The results showed that total CK activity in the patient’s skeletal muscle was only 3,500 IU/g wet weight, but 170,000 IU/g wet weight in control. In a blood sample from a healthy man, electrophoresis of the serum CK showed the bands of MM, MB and BB in that order from the cathodal side. In the patient’s serum, no CK isozyme band was detected. With the control skeletal muscle
sample, only the MM band was found and the fraction could be inactivated by addition of anti-CK-MM antibodies. In contrast, the electrophoresis of the sample obtained from the patient’s skeletal muscle did not show the MM band, but showed BB and an abnormal band migrating closer to the cathode than MM. This abnormal band was not inactivated by addition of anti-CK-MM antibodies. CK is known to be inactivated by heating at 50°C for 10 minutes (4); this abnormal cathodal band of the patient remained after heat treatment, whereas the CK-MM band of the control did not (Fig. 8). The mol wt of this abnormal band was estimated to be 300,000 K dalton by gel filtration.

To determine if the CK abnormality of this patient might be due to heredity, we determined the serum CK levels of his family. One of his sisters showed a marked low activity of serum CK, 2IU/l. Also as mentioned above, his father and elder brother had died suddenly at the ages of 60 and 56, respectively (Fig. 9).

**Fig. 7.** Thallium-201 stress myocardial scintigraphy after PTCA showing no hypoperfusion during stress in the anterior wall. The persistent defect in the inferior wall represents an old myocardial infarction (arrows).

**Fig. 8.** Electrophoretogram of CK isozyme. ① serum from a healthy man used to establish standard CK levels. ② control skeletal muscle. ③ addition of anti-CK-MM. ④ skeletal muscle of control. ⑤ heat treatment*. ⑥ skeletal muscle of patient. ⑦ addition of anti-CK-MM. ⑧ skeletal muscle of patient. ⑨ heat treatment. ⑩ serum from patient.

**Fig. 9.** Family history of the patient showing low CK activity in his younger sister (arrow) and sudden death (SD) of his elder brother and father. P: patient.
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Discussion

CK consists of two subunits, M (muscle type) and B (brain type). The CK isozymes can be separated electrophoretically as MM, MB, and BB from the cathodal side. CK-MM is found mainly in the skeletal muscle, CK-MB in the myocardium and CK-BB in the brain or the smooth muscle. In addition to these cytoplasmic CK, there is another CK localized in the mitochondria, the serum level of which is reported to increase in patients with malignant tumor (5). To maintain an ATP supply for muscle contraction and to reserve high energy phosphate, CK catalyzes Lohmann’s reaction: ADP + creatine phosphate « ATP + creatine. Determination of the serum CK level is of clinical value in the diagnosis of disorders of the skeletal muscle or myocardium.

The present patient had an extremely low serum CK activity of less than 5% of the normal value during acute myocardial infarction. Human skeletal muscle contains mainly CK-MM with small amounts of CK-MB. Total CK activity in the sample of the patient’s skeletal muscle was 2% of that of the control, and examination of the CK isozyme showed that only BB was present with no MM or MB. Goto et al. stated that skeletal muscle in the early fetal stage contains only BB and the conversion from BB to MB or MM takes place at about the third or the fourth month of gestation in the human fetus (6). Because CK-BB is often found in the serum of patients with malignant tumor, e.g. lung cancer or prostatic cancer, detection of serum CK-BB is considered to be of diagnostic values as a tumor marker (7-9), probably because of its relation to functionally immature tumor cells. Therefore, we speculate that the CK-BB found in the patient’s muscle may be associated with an abnormality in the process of CK differentiation. Electrophoresis of a patient’s skeletal muscle revealed an abnormal band which migrated cathodal to CK-MM, and was not inactivated by addition of anti-CK-MM antibodies and heat treatment. The mol wt of this band was estimated to be 300,000 by gel filtration. This band was speculated to be adenylate kinase, as it has similar mobility on electrophoresis and a similar molecular size. Adenylate kinase also contributes to the synthesis of ATP catalyzing the following reaction: 2ADP « ATP + AMP. Thus, the ATP formed by hydrolysis of ATP during contraction may be rephosphorylated by adenylate kinase. We did not determine the adenylate kinase directly by the method of Brolin (10), which is usually used. Another possibility for this fraction migrating more cathodically than CK-MM may be mitochondrial CK, as previously reported (11, 12). However this could not be clarified because we did not isolate the mitochondrial fraction from the patient’s skeletal muscle as described previously (13, 14).

Although the electrocardiogram during the exercise treadmill test revealed ST segment depression suggesting myocardial ischemia, the coronary angiogram showed no significant stenosis in the left coronary artery and 201-thallium stress myocardial scintigraphy did not show any hypoperfusion area in the anterior wall during stress. In addition, no significant lactate production was observed during atrial pacing in the examination of the myocardial metabolism. Thus there was no evidence of myocardial ischemia in this patient, and the amount of oxygen was sufficient to support production of ATP by oxidative phosphorylation in the mitochondria. It is not known whether ST segment depression on ECG during exercise was merely false positive or due to the effects of CK deficiency. We speculated that the myocardium of this patient might be able to contract with an extremely small amount of CK or with some compensation by another pathway or other enzymes such as adenylate kinase. Increasing the exercise level may gradually distinguish the influence of deficiency of CK on muscular contraction.

Finally, examination of the family showed that one of the sisters had a marked low serum CK level, suggesting inheritance of this abnormality. Although two male members of the family had died suddenly, the relationship between this and CK abnormality is not clear. To clarify the mechanism of energy supply in this patient, further investigations are needed.

Acknowledgments: We wish to especially thank Dr. Jiro Ohkawa, Chief of the Department of Pathology, Hyogo Medical Center for Adults, for his co-operation in this study.

References

