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CASE REPORT

Angina in McArdle's disease

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Abstract

McArdle's disease (myophosphorylase deficiency) results in the inability to metabolise skeletal muscle glycogen to lactate. A patient with this condition developed angina and therefore offered a unique opportunity to explore the differential expression of the defective myophosphorylase gene in skeletal and cardiac muscle.

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Keywords: McArdle's disease; myophosphorylase; lactate.

McArdle's disease is a rare glycogen storage disease (type V).[1] Typically patients describe the onset in childhood of severe cramp like pain in the muscles on exertion. Absent myophosphorylase (EC 2.4.1.1) activity in skeletal muscle prevents anaerobic metabolism and hence lactate formation. The use of alternative energy sources leads to ammonia formation and alkalosis on exertion.[2] A patient with McArdle's disease developed effort angina, and therefore offered a unique opportunity to compare the cardiac and skeletal muscle expression of the myophosphorylase gene.

Case report

A 66 year old man started with muscle pains on exertion as a teenager. The diagnosis of McArdle's syndrome was confirmed by raised serum creatine kinase concentrations, usually >1000 U/l; absent myophosphorylase activity and glycogen accumulation on muscle biopsy; typical cardiopulmonary and metabolic responses to exercise[2]; and heterozygosity for the nonsense mutation in exon 1 of the myophosphorylase gene on chromosome 11q.[3] In addition, he had gout and hypertension. For several months, exercise had been limited by chest pain rather than leg cramps.

Myocardial imaging was performed by injection of 55·5 MBq of ^{201}Th after infusion of dipyridamole (44 mg). Multiple perfusion defects were observed, some with reperfusion and some with impaired wash out. At coronary angiography, which showed severe triple vessel disease, a catheter was advanced from the right median cephalic vein to the coronary sinus and a bipolar pacing wire from the femoral vein to the right atrial appendage. Simultaneous blood samples were taken from the ascending aorta and the coronary sinus for lactate, pyruvate, and ammonia concentrations.[2] After two basal samples, the heart rate was increased by 10 beats/min every 2 min and samples withdrawn during the last 30 s of each pacing period.

Subsequent coronary artery bypass grafting produced marked symptomatic benefit. At operation, a small sample (about 300 mg) of right atrial muscle was removed, with the patient's prior consent. A similar sample for comparison was removed from a man aged 53 undergoing the same operation on the same day. Both samples were immediately plunged into liquid nitrogen and saved for subsequent phosphorylase isoenzyme analysis by polyacrylamide gel electrophoresis (PAGE).[4] Slab gels of 5% acrylamide were prepared in TRIS(42 mM)-borate (48 mM) buffer pH 8·2, EDTA (1 mM), and glycogen (0·1%). Electrophoresis was performed in a refrigerated chamber with LKB 2219 cooling system and LKB power supply, gels being pre-run at 260 V for 10–40 min. Tissue samples (about 15 mg) were homogenised in a glass-glass homogeniser with several volumes of β-glycerophosphate (40 mM) buffer pH 6·8, NaF (40 mM), EDTA (10 mM), and mercaptoethanol (20 mM) and centrifuged for 10 min at 10 000 *g*. The supernatant was diluted as necessary in phosphate buffered saline (pH 7·4) with added bovine serum albumin (0·5%), and applied to the gel in 10% sucrose solution. Electrophoresis was performed at a constant voltage (260 V) for 1 h. Gels were incubated overnight at room temperature in glucose-1-phosphate solution (2 mM), β-glycerophosphate (2 mM), pH 6·8, EDTA (2 mM), NaF (10 mM), 5'AMP (2 mM), and then stained briefly in iodine solution. Glycogen, β-glycerophosphate, glucose-1-phosphate, and 5'AMP were purchased from Sigma Chemical Co.

Results

Lactate concentrations during incremental pacing (table) increased in the coronary sinus

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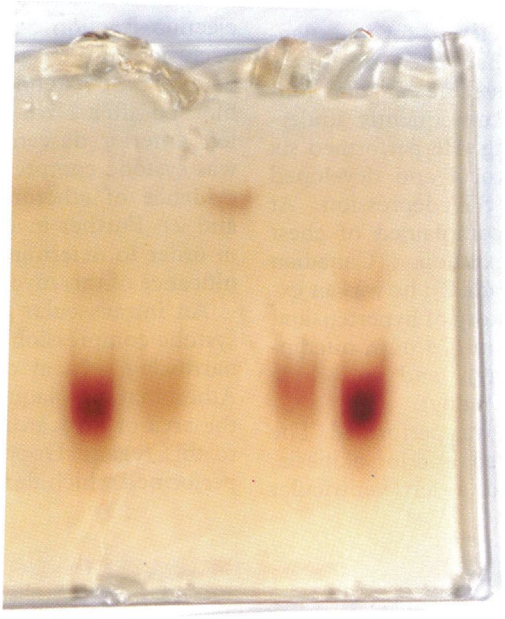
Blood lactate concentrations (mmol/l) in the ascending aorta (Ao) and the coronary sinus (CS) during incremental right atrial pacing, in a patient with McArdle's disease

Heart rate (beats/min)	*Ao*	*CS*
Before pacing:		
68	0·39	0·27
66	0·43	0·28
Paced:		
70	0·41	0·29
80	0·39	0·29
90	0·36	0·29
100	0·41	0·30
110	0·38	0·39
120	0·43	0·56
130	0·45	0·52
Recovery:		
3 min	0·45	0·40
6 min	0·41	0·34



Polyacrylamide gel electrophoresis of myophosphorylase isoenzymes in a cardiac biopsy from a normal control (NH) and the patient with McArdle's disease (PH). Also shown is the pattern from normal skeletal muscle (NS). Note that only the fast moving band was detected in the patient.

above a rate of 120 beats/min, reversing the A/V ratio, and coinciding with the onset of chest pain and electrocardiographic (ECG) abnormalities. These changes reversed during recovery. No changes were recorded in the plasma concentration of ammonia or pyruvate. Both the patient's and the control cardiac muscle biopsy showed normal histological appearances (including on electron microscopy). On histochemical staining, myophosphorylase activity of similar intensity was detected in both. PAGE (figure) showed that a major isoenzyme (the one normally found in skeletal muscle) was missing from the myocardial tissue of the patient.

Discussion

Human cardiac tissue contains three isoenzymes of myophosphorylase[4 5] which can be separated by PAGE. The slow migrating band (figure) corresponds to skeletal muscle activity, the intermediate band comprises both skeletal and cardiac muscle subunits, and the fast migrating band is found in cardiac tissue only. Patients with McArdle's disease lack the slow migrating band, the only isoenzyme found in skeletal muscle: but the presence of the other isoenzymes in cardiac tissue ensures that the genetic defect is expressed differently. It seems that the remaining myocardial myophosphorylase activity is adequate for all needs, and indeed it could be argued that a relative or absolute deficiency of lactate production from cardiac tissue would be fatal at an early age. The electrophoretic findings we observed are similar to those previously reported in an infant with the rare severe childhood form of McArdle's disease[4] but no studies of adults have been reported so far.

Patients with McArdle's disease are unable to mobilise skeletal muscle glycogen, which accumulates, and rely solely on circulating glucose and fatty acids as their main energy source. Anaerobic metabolism is very inefficient and exercise causes severe leg pain. Continued exercise may produce rhabdomyolysis and acute renal failure. However, apart from the inability to perform high levels of exercise, metabolism is otherwise normal, as is life expectancy, unlike most other patients with glycogen storage diseases.

There is no evidence of cardiomyopathy in McArdle's disease, although ECG abnormalities have been described.[6] Patients live long enough to develop degenerative vascular disease.[7] Indeed, such problems may be more likely to develop in this group of patients because of their excessive circulatory responses to moderate exercise loads.[8 9]

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