Case reports

on oral and intravenous glucose alone to maintain the blood glucose level, and the second was at the age of 10 weeks. Treatment had been stopped gradually by the age of 1 month as the infant's blood glucose was satisfactory, but the insulin levels had not returned to normal.

In future cases, treatment should include diazoxide and corticosteroids as soon as the diagnosis of hypoglycaemia is made. These drugs should be withdrawn slowly when the blood glucose level is satisfactory and the serum insulin levels are normal.

References


Lactate production in McArdle's disease

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Summary

A case of McArdle's disease in a man is described in detail and a less complete study of his family is reported. This patient showed the classical features of McArdle's disease and the diagnosis was confirmed by muscle biopsy. Unlike other reported cases of this disorder, this case showed a normal rise in blood lactate levels on ischaemic exercise. This apparently paradoxical finding is discussed. It is suggested that a normal rise in the level of blood lactate on ischaemic exercise should not exclude myophosphorylase deficiency.

Introduction

In 1951, McArdle reported the case of a 30-year-old man who had suffered from life-long muscular pain on slight exertion, progressing on continued exertion to weakness and stiffness. These symptoms usually disappeared on resting. Localized swellings in muscle and abnormal shortening of flexor muscles were seen to occur after ischaemic exercise. Electromyography showed that muscle shortening was a reversible physiological contracture of the muscle fibre not associated with any conducted action potential in the muscle. An important finding was the absence of the normal rise in blood lactic acid on ischaemic exercise. Subsequently, further cases were reported by Pearson, Rimmer and Mommaerts (1959), Schmid and Mahler (1959), Mellick, Mahler and Hughes (1962) and Schmid and Hammaker (1961), and in all instances the blood lactic acid level failed to rise on ischaemic exercise. Histochemical study of muscles from these patients
showed a marked reduction or complete absence of muscle phosphorylase.

The purpose of this communication is to report the case of a man who had all the features of McArdle's disease including absence of myophosphorylase, but in whom the level of blood lactate rose on ischaemic exercise.

Case report
A 27-year-old male was referred to one of us (R.R.H.) for investigation of periods of loss of consciousness. In 1959 he had had two such episodes, both occurring after heavy exertion. More recently he had suffered another attack following a particularly heavy session of weight-lifting. After this last episode he voided dark urine. None of these attacks was preceded by any aura, nor associated with convulsions, tongue biting or incontinence. He also stated that for as long as he could remember he had had 'trouble with his muscles' on exertion. Whilst at rest he was comfortable but on moderate exertion his muscles ached and became weak. He was unable to walk up-hill for more than a short distance and at school he could only run about 100 yards before he was forced to stop because of muscle cramps. Latterly, he and his wife had taken up weight-lifting and he stated that he could only lift the weight a few times while his wife could go on lifting for much longer. After these exercises his muscles developed painful cramps and weakness. On several occasions he had voided dark urine, and one such episode was noted after vigorous physiotherapy whilst in hospital; it persisted for several days and was accompanied by muscle tenderness. Urinalysis had confirmed the presence of myoglobin.

Physical examination was normal. There was no muscle wasting and the reflexes were normal.

Investigations
Ischaemic exercise tests were carried out according to McArdle (1951).

Method
The tests were performed with the patient in a fasting state. He lay on a couch for 30 min before
Electromyography (with a needle electrode in the right abductor digitus minimus muscle) was normal. A cuff was applied to the upper arm at 130 mmHg pressure and the patient was then asked to grasp and relax his fingers around a sphygmanometer bulb. After 30 sec he developed a sustained 'contracture' of the forearm muscles. This was not associated with any electrical activity.

Muscle biopsy and histochemistry. A motor-point biopsy was performed under local anaesthesia on the palmaris longus muscle. Conventional stains showed more variation than normal in the size of muscle fibres with an increase in muscle fibres with central nuclei. Occasional sub-sarcolemmal clear blebs were seen and in some areas there was a slight increase in collagen between groups of muscle fibres.

Frozen sections stained by Best's carmin method for glycogen showed some increase within the muscle fibres generally, and some homogeneous material, also staining for glycogen, outside the sarcolemmal sheath. Digestion by salivary amylase confirmed this to be glycogen. A muscle biopsy on a patient with vascular disease done at the same time showed no excess of glycogen.

Muscle enzymes. Cryostat sections were examined for NADH-tetrazolium reductase (DPNH diaphorase), myophosphorylase (using the method of Takeuchi and Kuriati, 1955) and adenosine triphosphatase routine reaction at pH 9·4. Myophosphorylase appeared to be completely absent but DPNH diaphorase and ATPase showed the presence of type I and type II muscle fibres in approximately equal proportions although rather more of the small fibres were type II.

Biochemical analysis of muscle showed myophosphorylase of 12 μmol/min/g (control, 116 μmol/min/g) and muscle glycogen of 2·36 g/100 g (control, 0·61 g/100 g).

Results of other investigations. Serum creatine kinase 2800 mi.u./ml (normal 0-130 mi.u./ml); serum lactate dehydrogenase 510 mi.u./ml (normal 200–400 mi.u./ml); serum aspartate amino-transferase 189 mi.u./ml (normal 8–40 mi.u./ml); serum alanine amino-transferase 155 mi.u./ml (normal 8–40 mi.u./ml); serum aldolase 97 μmol/min/l (normal 1·5–12 μmol/min/l); serum bilirubin 0·8 mg/100 ml. serum alkaline phosphatase 3·5 KA units/100 ml; serum protein-bound iodine 7·6 μg/100 ml; plasma cortisol 14·5 mg/100 ml; fasting serum calcium 9·5 mg/100 ml; serum inorganic phosphate 4·1 mg/100 ml; serum creatinine 1·0 mg/100 ml, creatinine clearance 70 ml/min; plasma bicarbonate 30 mmol/l, plasma potassium 4·7 mEq/l; plasma sodium 138 mEq/l; plasma urica 31 mg/100 ml; haemoglobin 15·8 g/100 ml; PCV 45%; WCC 5000/mm³.

| Table 1. Results of ischaemic exercise tests |
|-----------------|----------------|---------------|
|                | Blood lactate | Urinary myoglobin | Control Blood lactate |
|                | (mg %)        |                | (mg %)             |
| (1) Pre-exercise | 11            | Absent         | 28                  |
| Post-exercise   | 22            | Positive       | 40                  |
| (2) Pre-exercise | 9·6           | Absent         | 8                   |
| Post-exercise   | 16            | Positive       | 11                  |

Fig. 3. To show normal ATPase at pH 9·4 in propositus.

and during the observations. Blood was withdrawn without stasis from the right antecubital vein. A cuff around the wrist was inflated to a pressure of 180 mmHg (the patient's blood pressure was 100/70 mmHg) to prevent the admixture of blood from the hand. A cuff around the right upper arm was then inflated to 180 mmHg. The right hand was exercised by rapid hard squeezing of an inflated sphygmanometer cuff and this was continued until the patient had to stop because of pain. Venous blood was taken from the right antecubital vein 10 sec after deflating the arm cuff. The results are shown in Table 1.
Family study

The patient has three children, all of whom are healthy. The parents of the propositus were not related. Neither parent had ever suffered muscular symptoms and examination was normal. The ischaemic exercise tests were normal in both parents.

Sib, aged 24 years, has been free from symptoms and healthy. No investigation was carried out on him.

Sib, aged 21 years, has had symptoms for as long as he could remember, and at school, whenever he played with other children, weakness had always forced him to rest before the others. Three years ago, while he was moving heavy furniture his muscles became stiff and painful, and he developed a ‘swelling over the back’. These symptoms subsided after a day. Two years ago he was involved in a fight, and his ‘entire body became painful and stiff’. On this occasion he passed very dark urine for the next three days. During the past 2 years he has been careful to avoid heavy exercise and has remained symptom-free. Physical examination was normal. He refused an ischaemic exercise test. His serum creatine kinase was 2550 mi.u./ml, SLDH 330 mi.u./ml, SGOT 47 mi.u./ml, and serum aldolase 70 μmol/min/l.

Sib, female, aged 16 years, was symptom-free, and examination was normal. The ischaemic exercise test showed a pre-exercise blood lactate level of 16 mg/100 ml and the level remained the same after exercise. Muscle biopsy was refused.

Sib, aged 7 years, did not admit to any symptoms. However, her mother stated that whenever she accompanied her to the shops, her daughter would pause quite frequently because of ‘tiredness’. Physical examination was normal. Investigations were refused.

Discussion

The clinical features of the case reported are classical of McArdle’s disease and the diagnosis confirmed by the marked reduction of myophosphorylase. However, the propositus herein reported showed a normal rise of blood lactate on ischaemic exercise.

Glycogen is broken down to glucose-1-phosphate as a first step in its degradation to pyruvate. Under anaerobic conditions pyruvate is changed to lactate. The enzyme responsible for the conversion of glycogen to glucose-1-phosphate is phosphorylase. Thus, in the absence of myophosphorylase glycogen breakdown cannot proceed and therefore lactate increase on ischaemic exercise does not occur in McArdle’s disease.

In the patient here described, it is possible that the muscles have developed adaptive measures to use blood glucose and other substrates from the circulation, thereby obviating the necessity for glycogen breakdown in muscle. Other authors have demonstrated that in McArdle’s disease intravenous infusions of fructose or glucose produce significant elevations of blood lactate level on ischaemic exercise and also result in increase in the exercise tolerance. Another pathway of glycogen degradation may be by the hydrolytic enzyme, amylo-1,4-glucosidase. This enzyme breaks down glycogen to free glucose which, in the presence of intracellular hexokinase and ATP, enters the glycolytic pathway without the mediation of phosphorylase. The increase in muscle glycogen in McArdle’s disease is not as prominent as in other glycogen-storage disease. This would suggest either decreased glucogen synthesis or, more probably, alternative pathways of glycogenolysis in muscles of patients with McArdle’s disease.

A history of cramps on exertion, the demonstration of muscle ‘contracture’ and the passage of dark urine due to myoglobinuria would make the diagnosis of McArdle’s disease very likely. The case described in this paper would suggest that a normal increase in blood lactate level on ischaemic exercise test should not be used to exclude myophosphorylase deficiency. The diagnosis is confirmed by demonstrating the absence or marked reduction of phosphorylase in muscle.

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