Cardiac Enzyme Changes in Myxedema Coma

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A 74-year-old man with myxedema and hypothermia had increased activities in plasma of creatine kinase (EC 2.7.3.2), aspartate aminotransferase (AST; EC 2.6.1.1), and lactate dehydrogenase (LD; EC 1.1.1.27) and increased proportions of CK-MB (up to 20% of total CK) and LD1 isoenzymes, but no clinical or investigational evidence of associated myocardial infarction. This case illustrates that plasma enzyme activity and isoenzyme profiles in such clinical settings should be interpreted with caution, because increases in CK-MB and LD1 may relate to myxedema coma or hypothermia (or both) rather than to myocardial infarction.

Estimation of the enzymes CK, AST, and LD is useful in diagnosing myocardial infarction and monitoring its progress. For improved diagnostic sensitivity, the isoenzymes CK-MB and LD1, which predominantly but not exclusively originate from cardiac muscle, are determined.

The activity of these enzymes in plasma can increase variably in hypothyroidism and hypothermia, usually by release from skeletal muscle (1). Knowledge of this is important in excluding myocardial infarction for such patients, whose route and dose of thyroid-replacement therapy are influenced by their cardiac status.

We report a case of myxedema coma where CK, AST, and LD activities were all increased, as were the proportions of CK-MB and LD1 isoenzymes. There were no clinical or other investigational findings of associated myocardial infarction. The activity of total CK and CK-MB declined rapidly from the time of admission, but the percentage of CK-MB, higher than usually observed in myocardial infarction, remained high. The slow decreases in total LD and AST activity, and the continuously increased LD1/LD2 ratio, were more typical of the enzyme changes in hypothyroidism associated with hypothermia. There have been reports that the isoenzyme LD1, usually associated with cardiac muscle, may be increased in hypothyroidism (2, 3).

To our knowledge, there have been no reports of hypothyroidism with CK-MB activity so increased as to be confused clinically with myocardial infarction.

Methods

Electrolytes, urea, creatinine, and CK, AST, and LD were measured with a SMAC II AutoAnalyzer (Technicon Equipment, Sydney, Australia), with Technicon reagents and methods. Between-run CVs for the three enzymes in low and high concentrations in controls were always <7% and usually <4%. Residual CK-B subunit activity was measured with a Cobas Bio centrifugal analyzer (Roche Diagnostics, Sydney, Australia), with the "CK-MB (NAC-act)" kit (Boehringer Mannheim GmbH, Mannheim, F.R.G.). CK and LD isoenzymes were separated by use of the "Paragon" electro-

Table 1. Cardiac Enzyme Changes in Myxedema

<table>
<thead>
<tr>
<th>Elapsed time, h</th>
<th>CK-MB (%)</th>
<th>CK (25-200)</th>
<th>AST (9-43)</th>
<th>LD (110-200)</th>
<th>LD1/LD2 ratio (&lt;0.76)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>11</td>
<td>1740</td>
<td>257</td>
<td>895</td>
<td>1.20</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>1440</td>
<td>245</td>
<td>—</td>
<td>—</td>
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<tr>
<td>15</td>
<td>19</td>
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<td>210</td>
<td>810</td>
<td>1.25</td>
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<tr>
<td>27</td>
<td>19</td>
<td>489</td>
<td>184</td>
<td>650</td>
<td>1.19</td>
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<tr>
<td>43</td>
<td>20</td>
<td>281</td>
<td>141</td>
<td>609</td>
<td>1.24</td>
</tr>
<tr>
<td>112</td>
<td>10</td>
<td>104</td>
<td>96</td>
<td>605</td>
<td>1.21</td>
</tr>
<tr>
<td>140</td>
<td>—</td>
<td>126</td>
<td>75</td>
<td>607</td>
<td>1.19</td>
</tr>
<tr>
<td>1 month</td>
<td>&lt;2</td>
<td>63</td>
<td>27</td>
<td>204</td>
<td>0.47</td>
</tr>
</tbody>
</table>

* Time since first venepuncture. * Percent of total CK. * Reference range at our laboratory. * Insufficient sample available to perform that particular test.

Received November 3, 1986; accepted January 12, 1987.

phoresis system (Beckman Instruments, Sydney, Australia) and the bands were quantified with a "Cliniscan" densitometer (Helena Labs, Beaumont, TX). Thyroxin was measured by an in-house RIA procedure, triiodothyronine by the "Amerlex-T3" RIA (Ameraham, Sydney, Australia), and thyrotropin by an immunoradiometric method (Seron Diagnostics, Woking, U.K.).

Case Report

The patient, a 74-year-old Anglo-Indian man, had experienced an episode of jaundice at age 40, after which he ceased cigarette and alcohol consumption. He had since adhered strictly to a Pritikin diet, took kelp and vitamins daily, and kept fit by running approximately 5 km daily. Over the two winter months before admission, he felt unusually aware of the cold. He suffered progressive loss of energy and exercise tolerance, and he developed swelling of his face and lower limbs. In the last two weeks before admission he became sleepy, confused, and mildly ataxic. Apart from short periods when he would try and jog in the room, the three days before admission were spent in bed. Three days prior to admission he was treated with a diuretic (furosemide, 40 mg daily) and a sedative (Percyazine, 2.5 mg three times daily). At admission he was stuporous. His family was adamant that he had not complained of any chest pain and that he had no previous history of myocardial infarction, facts later confirmed by the patient.

On examination, he was hypothermic (rectal temperature 31°C), bradycardic, normotensive, and stuporous, and he had depressed reflexes with delayed relaxation. His muscles were markedly pseudomyotonic. An initial measurement of plasma sodium was 118 mmol/L (reference interval 134–146 mmol/L), potassium 2.8 mmol/L (3.4–5.0), total CO2 30 mmol/L (22–32), urea 4.1 mmol/L (3.0–8.0), creatinine 51 μmol/L (50–120), and initial enzyme values as shown in Table 1. Plasma osmolality was 241 mosmol/kg (275–295), urinary sodium was 41 mmol/L (untimed sample), and urine osmolality was 445 mosmol/kg.

The initial electrocardiogram showed nonspecific ST flattening, a sinus bradycardia of 46/min, and small QRS complexes. The QT interval was prolonged to 0.60 s (expected 0.43 s) and there were no Q waves present. Daily
electrocardiograms demonstrated no Q waves, resolution of the bradycardia, and a return of the QT interval to the normal range.

Chest roentgenography revealed normal heart size, with some patchy consolidation in the right middle lobe. Blood cultures grew *Acinetobacter* species sensitive to amoxycillin and gentamicin.

The patient was treated initially with insulated blankets and intravenous fluids; 18 h after admission intravenous amoxycillin and gentamicin were administered. He was given thyroxin, 200 μg daily, and triiodothyronine, 20 μg three times daily. Initially, hydrocortisone was given intravenously (100 μg, three times daily). He quickly responded to this regime and was walking around within 36 h of initiating treatment with triiodothyronine. Thyroid-function tests, done on blood obtained before treatment, confirmed the diagnosis of hypothyroidism: the serum thyroxin concentration was 14 nmol/L (reference interval 70–140 nmol/L), triiodothyronine 0.6 nmol/L (1.1–2.6), and thyrotropin 60 milli-int. units/L (0.5–6.0). The cortisol concentration in this specimen was 662 nmol/L (reference interval 150–500). The patient’s hyponatremia responded rapidly to the treatment of the myxedema. (Hyponatremia, a common finding in severe hypothyroidism, is probably due to decreased excretion of free water as well as inappropriate secretion of antidiuretic hormone (vasopressin) (4).)

Table 1 shows the enzyme and isoenzyme profiles. CK activity decreased from the time of admission, the half-life for the disappearance being 17 h, which suggested an acute pre-admission release of intracellular material from damaged tissue. This finding, along with the above-normal CK-MB activity, initially raised the possibility of myocardial infarction. However, as the CK activity declined, the proportion of CK-MB isoenzyme remained high. Because the biological half-life of CK-MB is shorter than that of CK-MM, the CK-MB proportion of total CK usually declines more rapidly than does CK-MM (5).

LD and AST activities decreased slowly as the disease was treated. Values for total LD became constant at an abnormally high activity and the LD1/LD2 ratio remained constant, also at an abnormally high value.

In view of his apparent cardiac enzyme abnormalities the patient was extensively investigated with regard to his myocardium. A two-dimensional echocardiogram revealed mild concentric left ventricular hypertrophy. There was no pericardial effusion, the heart valves and chambers were normal, and in particular there was no evidence of any regional abnormality of wall motion. A technetium pyrophosphate radionuclide scan showed no evidence of a recent myocardial infarction, and radionuclide angiography with use of technetium-labeled erythrocytes showed a normal ejection fraction with normal wall motion.

He was discharged eight days after admission with instructions to take L-thyroxin, 150 μg daily. Thyroid-function tests at discharge showed thyroxin 102 nmol/L, triiodothyronine 1.5 nmol/L, and thyrotropin 9.3 milli-int. units/L.

In the outpatient clinic one month after discharge, he showed no clinical abnormalities, and results for his thyroid-function tests and enzyme and isoenzyme profiles had all returned to within our quoted normal reference intervals (see Table 1).

**Discussion**

Myopathy associated with hypothyroidism is a common finding and usually responds rapidly to treatment. Electron-microscopic examination of skeletal muscle in a group of hypothyroid patients with myopathy (6) showed various degrees of structural changes directly correlated with the severity of the hypothyroidism. The patients with the most severe myopathy showed Type II muscle fibre loss and atrophy, increased numbers of mitochondria, and accumulation of glycogen and lipid on membranes. The latter findings implied an acquired defect in lysosomal enzymes, affecting in particular glycogenesis and glycogenolysis and possibly membrane-stabilizing enzymes. All these structural and biochemical changes were reversible with adequate treatment. Therefore it is not surprising, with these changes in muscle, that plasma CK and LD are increased in hypothyroidism. In some series, as many as 80% of patients with primary hypothyroidism may show this pattern (3).

The increased LD values seen in hypothyroidism are more often due to increases in LD6 (principally of skeletal muscle origin), but increases in LD1 are not uncommon (2). It has been shown that LD leaks from peripheral blood leukocytes from hypothyroid patients (7), and it has also been suggested that altered permeability of erythrocyte membranes may explain the increase seen in hypothyroidism (8). However, our patient was not anemic, his hemoglobin concentration remaining around 121 g/L, a normal value for mean cell volume of 94 fl (82–98 fl), normal values for serum B12 and folate, and normal differential blood-cell counts. It therefore seems unlikely that leakage from erythrocytes or leukocytes was responsible for the marked LD isoenzyme changes observed. Increased LD1 is sometimes seen in a variety of malignancies (9). However, no clinical suggestion of malignancy was found, and after one month of thyroxin replacement his LD isoenzyme pattern had returned to normal.

All studies of CK isoenzymes in hypothyroidism have shown that CK-MM is predominant and that CK-MB, if present, is in low proportions consistent with the trace amounts in skeletal muscle, and not capable of causing diagnostic confusion as to the source of the enzyme (10–12). Our patient had CK-MB values varying between 10 and 20%—see Table 1. (Both electrophoresis and immunoinhibition studies were performed. The results were similar and, for convenience, only the results by electrophoresis are shown.) We confirmed the identity of the band with apparent CK-MB electrophoretic mobility as before (13) by preincubating samples with anti-M before electrophoresis. The CK-MM and CK-MB bands disappeared, to be replaced by a diffuse fluorescence near the application point.

Several aspects of this case make a diagnosis of myocardial infarction unlikely. Firstly, CK-MB proportions as high as 20% are unusual in myocardial infarction, particularly at a time when total CK activity is declining. Secondly, the slow decrease of AST and LD and the plateauing of LD are not found in myocardial infarction. Thirdly, despite extensive clinical and laboratory investigation, no evidence of myocardial infarction could be found. We believe that this man did not have a myocardial infarct and that the finding of an increased CK-MB represents either non-myocardial infarct release from cardiac muscle or ectopic synthesis of CK-MB.

Cardiomyopathy, with cardiomegaly, cardiac failure, and effusions are not uncommon findings in hypothyroidism. It is conceivable that an altered membrane permeability similar to that found in hypothyroid skeletal muscle could have caused the increased CK-MB values seen. Our patient, however, had only minor signs relating to his cardiovascular system, and his rapid clinical improvement in the presence.
of continuing abnormalities of AST and LD makes this possibility unlikely.

There are now many reports of CK-MB being synthesized in significant quantities in skeletal muscle, in conditions where there is chronic tissue regeneration or injury, such as muscular dystrophy (14) and polymyositis (15). In addition, above-normal values for CK-MB have been found in association with malignant disease (13, 16). Thus, increases in CK-MB are not myocardium-specific, a point reinforced by Ingwall et al. (17).

Significantly increased proportions of CK-MB, ranging from 7 to 32%, with variably increased total CK activity, have been reported in patients with hypothermia per se (18). Warming hypothyroid patients (19), or resting ambulatory people (20), can produce marked drops in CK activity and may in part explain the rapid fall in CK activity observed in our patient.

It is not possible from our data to state categorically whether the enzyme changes observed relate specifically to myxedema coma, to hypothermia, or both. However, the unusual exercise activities of this patient with pseudomyotonia suggest that they are more likely to be related to hypothyroid myopathy and in this context the increase in CK-MB is a unique finding.

References