Hypoglycemia and lactic acidosis associated with fructose-1,6-diphosphatase deficiency

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Hereditary fructose-1,6-diphosphatase deficiency is an inborn error of carbohydrate metabolism characterized by metabolic acidosis, hyperventilation, fasting hypoglycemia, and hepatomegaly. Acidosis is associated with elevated lactic, pyruvic, beta-hydroxybutyric, and acetoacetic acids. Hypoglycemia and acidosis may be induced in affected children by prolonged fasting or by infections, and by administration of fructose, glycerol, or alanine. Prevention of hypoglycemia and acidosis has been reported with a fructose-free diet and with folic acid therapy. We report a child who presented with recurrent lactic acidosis and hypoglycemia associated with fructose-1,6-diphosphatase deficiency in whom we have tried both diet and folate therapy.

CASE REPORT

The subject was a male infant born of healthy parents. Diarrhea at 6 months of age led to lethargy, hyperpnea, and seizure activity. The child appeared gravely ill, was semicomatose, and had hepatomegaly. Pneumonia was diagnosed by X-ray study (for laboratory studies, see Table I). The infant was treated with intravenous fluids, bicarbonate and antibiotics, and given a transfusion for gastrointestinal blood loss thought to result from a stress ulcer. Over the next year, several episodes of mild metabolic acidosis were encountered with intercurrent infections, though the child appeared healthy and had no noticeable symptoms in the intervals between infections. The hepatomegaly gradually decreased.

At 18 months, with tonsillitis and fever, the subject began vomiting, became lethargic, and had tachypnea (50/minute). Again he appeared very ill and had pronounced hepatomegaly. In addition to the studies shown in Table I, the salicylate level was 0 and the serum ketone concentration was greater than 12 mg/dl. The subject again responded to treatment with bicarbonate and intravenous fluids.

At 20 months, he was admitted to the University of Utah Medical Center for evaluation of recurrent acidosis and suspected adrenal insufficiency. Adrenal response to ACTH was found to be normal, with a rise of plasma cortisol from 14 to 40.8 μg/dl. During the hospitalization, lethargy and hyperpnea occurred in conjunction with an otitis media (see Table I for laboratory studies). Because of an anion gap greater than 20 mEq/l, lactate was measured and found to be 101 mg/dl (normal 5 to 20 mg/dl). There was also elevation of serum pyruvate, acetoacetate, and uric acid. A glucagon stimulation test produced a normal rise in serum glucose concentration. Because of persistent hepatomegaly, a percutaneous liver biopsy was performed. The biopsy showed fatty deposits but no abnormal glycogen storage.

Subsequent studies of the lactic acidosis led to a recognition of fructose intolerance and a defect in gluconeogenesis. Treatment with frequent feedings free of fructose resulted in clinical improvement, as described below.

METHODS

All tests were performed on our Clinical Research Center with informed consent of the parents. After an overnight fast of 8 hours, glucose was administered orally in a dosage of 2 gm/kg. Blood samples were obtained at 0, 30, 60, 120, and 180 minutes. Glucose (AutoAnalyzer), lactate, pyruvate, and acetone were performed through hospital or commercial laboratories. For glucagon stimulation, 30 μg/kg of glucagon was administered intramuscularly, both in the fed and fasted state. Blood samples were obtained at 20-minute intervals for glucose, lactate, and pyruvate.

Glycerol was administered orally (1 gm/kg) with blood

Table I. Clinical laboratory data

<table>
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<th>Age of subject (mo)</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Cl⁻</th>
<th>HCO₃⁻</th>
<th>pH</th>
<th>BS</th>
<th>LDH</th>
<th>SGOT</th>
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<td>6</td>
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<tr>
<td>19</td>
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<td>104</td>
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<td>20</td>
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<td>99</td>
<td>&lt;5</td>
<td>472</td>
<td>500</td>
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</table>

BS = Blood sugar; LDH = lactic dehydrogenase; SGOT = serum glutamic oxalacetic transaminase.

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samples at 0, 10, 30, and 60 minutes for measurement of glucose, lactate, and pyruvate. Following ingestion of a 50-gm fatty meal, blood was obtained at 30 minute intervals for lactate and pyruvate. Ketones were measured in the urine by Ketostix.

Fructose was administered in a dosage of 0.2 gm/kg intravenously. Blood samples were obtained at 0, 10, 20, 30, and 45 minutes for measurement of reducing substances, lactate, pyruvate, and bicarbonate. During prolonged fasting, blood was obtained at three- to four-hour intervals for measurement of glucose and lactate until hypoglycemia or acidosis prompted cessation of testing.

Needle biopsy of the liver was performed after an eight-hour fast. Tissue was preserved in formalin and alcohol for histologic preparations. Open liver biopsy was performed with the patient under general anesthesia after an eight-hour fast with administration of 5% dextrose in water. Tissue was frozen at −70°C in liquid nitrogen. The tissue was shipped frozen with dry ice to the collaborating laboratory for enzyme assays. On the biopsy specimen (performed by B. I. Brown, St. Louis) the following enzymes were determined: glucose-6-phosphatase, liver phosphorylase, fructose-1,6-diphosphatase, FDP-aldolase, and fructose-1-phosphate aldolase by methods previously described.4

**RESULTS**

Following a glucose load, a normal response of blood glucose was noted; although modestly elevated at the beginning of the test, no change in lactate of pyruvate was noted. Glucagon stimulation following a 12-hour fast failed to produce a rise in blood glucose, in contradistinction to a normal rise noted without a fast. Lactate levels rose only modestly (from 23 to 31 mg/dl) following glucagon in the fed state, whereas a rise to 68 mg/dl was documented after administration of glucagon following a 12-hour fast. Lactate and pyruvate levels doubled after exercise and returned slowly toward normal after a 60-minute period of inactivity.

Following intravenous infusion of fructose, total reducing substance in the blood fell rapidly from a high of 235 mg/dl to a low of 15 mg/dl within 45 minutes. This was accompanied by a rise of serum lactate and serum pyruvate values, a fall in serum bicarbonate, and by hyperpnea (Table II). After a 12-hour fast, glycerol was administered orally (1 gm/kg). A drop in glucose to hypoglycemic levels was noted by 60 minutes, and there was a concomitant rise in lactate with a paradoxical decrease in pyruvate (Table II).

From the liver tissue obtained during exploration, glucose-6-phosphatase, liver phosphorylase, fructose-diphosphate aldolase, fructose-1-phosphate aldolase, and pyruvate kinase enzymes were all found to be normal, whereas fructose-1,6-diphosphatase activity was absent (Enzyme assays performed by B. I. Brown, St. Louis).

Treatment with a fructose-free diet resulted in considerable clinical improvement. During subsequent illnesses from childhood infections, prompt use of corn syrup prevented acidosis and hypoglycemia which earlier led frequently to hospitalization. Addition of folate therapy (2 mg/kg/day) failed to produce further clinical improvement. Increase of the folate to 20 mg/kg/day produced no noticeable change. Ability to tolerate prolonged fast with hypoglycemia did improve with time and/or fructose-free diet, but seemed unchanged by the addition of folate. Hypoglycemia occurred at about 12 hours during early testing, but increased to about 16 hours during later tests after therapy with diet or folate therapy (Figure). In all instances, a decrease in blood sugar was accompanied by
an increase in lactate. Therapy failed to change the response to glucagon, which failed to produce any elevation of blood glucose after a prolonged fast.

**DISCUSSION**

Deficiency of fructose-1,6-diphosphatase results in a metabolic acidosis associated with lactic acidemia, hypoglycemia, and hepatomegaly. In addition, some observers have reported hyperventilation and elevated pyruvate, ketone, and uric acid concentrations. Hypoglycemia is noted to occur in the fasting state, with diminished or absent response to glucagon after a fast. Hypoglycemia and lactic acidosis occur after administration of fructose, glycerol, glycerol, dihydroxyacetone, or alanine. Severe acidosis has been provoked by sorbitol administration. In one report, hypoglycemia was said to occur after administration of glucose and galactose, but in all other reports a normal response to glucose was noted. Jaundice and hypoponemia were reported in one subject. Liver function has generally been normal. A deficiency of hepatic fructose-1,6-diphosphatase activity is always demonstrable in affected children, whereas fructose aldolases and enzymes of glycolysis are normal.

When fructose (or other gluconeogenic substrates such as glycerol or alanine) is administered to a subject with FDPase deficiency, there is a rapid fall in blood glucose and development of a lactic acidosis. The cause of the lactic acidosis is readily appreciated from the known disruption in gluconeogenesis. The rapid development of hypoglycemia cannot be satisfactorily explained by a block in gluconeogenesis alone. In the absence of any increase in serum insulin, interference with glycolysis has been postulated to explain the sudden hypoglycemia. Phosphorylase activity has been shown to be inhibited by fructose-1-phosphate and fructose-1,6-diphosphate, substrates which have been shown to accumulate with FDPase deficiency. It is likely, therefore, that the hypoglycemia is a result of a block of both gluconeogenesis and glycolysis.

The biochemical response in FDPase deficiency suggests that treatment should include avoidance of a prolonged fast and of fructose ingestion. Others have stressed a diet proscribing fructose (i.e., fruits), sucrose, honey (an invert sugar containing glucose and fructose), and sorbitol. Clinically, there was noticeable improvement in our patient on a fructose-free regimen. During illnesses which decreased food intake, the use of corn syrup (which contains mainly maltose) prevented clinical hypoglycemia and acidosis.

Folic acid was suggested by Greene et al for treatment of ketotic hypocemia in which a mild deficiency of FDPase had been documented. In patients with mild FDPase deficiency, tolerance to fructose, glyceral, and alanine without hypoglycemia was noted after folate therapy. Use of fructose-free food and avoidance of prolonged fasting were of benefit in our patient, but we were not successful in altering our patient's tolerance to fasting with folate therapy, nor in improving his clinical response to illness.
REFERENCES


Psychosocial problems as the major complication of an adolescent with trimethylaminuria

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Among the diseases associated with a peculiar body or urine odor, only one, trimethylaminuria, is described as having no complications with regard to growth and development. This report, however, describes the complications of social rejection, poor school performance, and mild depression in an adolescent with trimethylaminuria. With early detection of his disease, based on the characteristic urine and body odor, the above mentioned complications would not have occurred.

CASE REPORT

A 13-year-old white boy was seen in the Pediatric Outpatient Clinic with the chief complaint of “bad body odor.” Since the age of 9%, the patient had been seen on 11 occasions for a similar complaint. At each visit the odor of foul smelling feet was noted, and the parents were told that this was a common problem in boys and could only be managed by good personal hygiene, deodorants, and special foot care to include not wearing tennis shoes. Despite vigorous attention to this advice, the boy continued to suffer socially from an almost intolerable body odor. A family history revealed no similar problems in two younger female siblings, or in his mother and father and their siblings or parents.

A social history revealed that the patient had been an outstanding student in both academic and leadership abilities until he entered the seventh grade. At that time his grades began to deteriorate; in addition, he was involved in many classroom and playground fights and dismissals from school, all of which centered around the constant ridicule he received about his body odor. At the time of this visit his mother related that he had no friends, spent his time out of school in his room, and appeared to her to be overtly depressed. She also related that at this time they were attempting to sell their home but potential buyers were distracted by an overpowering smell of dead fish in all rooms of their home. Six buyers had rejected the house simply on the basis of the smell alone; this fact had led to further guilt feelings and depression in the patient.

Physical examination revealed a very quiet and somewhat introverted adolescent boy; the remainder of the physical examination was entirely normal except for an overpowering odor similar to that of putrid fish. The odor was present over the entire body but was most noticeable on his feet and axillae. The putrid fish odor suggested a possible defect in trimethylamine metabo-