ACID-BASE AND ELECTROLYTE TEACHING CASE

Neonatal Acidosis With Nephrocalcinosis: A Clinical Approach

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INDEX WORDS: Glycogen storage disease; infant; lactic acidosis; nephrocalcinosis.

Persistent metabolic acidosis with increased anion gap during infancy is a strong indicator of an underlying metabolic disorder. Association of acidosis with nephrocalcinosis is uncommon and occurs primarily in patients with renal tubular disorders. We present an infant with lactic acidosis, nephrocalcinosis, and hyperlipidemia caused by glycogen storage disorder type I and discuss pertinent issues.

CASE REPORT

Clinical History

A 4-month-old girl presented to the outpatient clinic with failure to thrive and polyuria since 1 month of life. The baby was a product of nonconsanguineous marriage and was born to a 23-year-old primigravida through the vaginal route. The antenatal period of the mother was uneventful. The delivery was at term, birth weight of the baby was 3.2 kg, and Apgar score was 7, 8, and 9. Polyuria, polydipsia, and irritability were noticed by the parents at around 1 month of age. There was no history of tachypnea, lethargy, poor feeding, vomiting, jaundice, or abnormal odor from body fluids.

On examination, the child was alert, but irritable, emaciated, afebrile, and pale. There was no icterus, cyanosis, cataracts, or rash. She had a heart rate of 120 beats/min and respiratory rate of 44 breaths/min. Recorded blood pressure was 70/50 mm Hg. She had a soft hepatomegaly 4 cm below the costal margin. The rest of the physical examination findings, including funduscopic evaluation, were normal. The weight of the child was 3.5 kg (<3rd centile), length was 52.8 cm (<3rd centile), and head circumference was 36 cm (<3rd centile). Laboratory tests showed a hemoglobin level of 8.8 g/dL (88 g/L) and total leukocyte count of $12.4 \times 10^3/\mu L$ (12.4×10^9/L; polymorphs, 28%; lymphocytes, 61%; monocytes, 7%; and eosinophils, 4%). Serum urea nitrogen level was 19.27 mg/dL (6.88 mmol/L), serum creatinine level was 0.7 mg/dL (61.8 mmol/L), uric acid level was 7.4 mg/dL (440 μmol/L), serum calcium level was 10.8 mg/dL (2.69 mmol/L), and phosphorous level was 6.2 mg/dL (2.0 mmol/L). Estimated creatinine clearance using the Schwartz formula was 41.5 mL/min. Liver function tests showed alanine aminotransferase level of 39 IU/L, aspartate aminotransferase level of 31 IU/L, serum alkaline phosphatase level of 100 IU/L, total protein level of 6.4 g/dL (64 g/L), and albumin level of 4.3 g/dL (43 g/L). Random blood glucose level was 70 mg/dL (3.9 mmol/L). The serum had a lipemic appearance; hence, a complete lipid profile was performed, which showed a cholesterol level of 239 mg/dL (6.18 mmol/L), triglyceride level of 996 mg/dL (11.24 mmol/L), high-density lipoprotein cholesterol level of 35 mg/dL (1 mmol/L), and very low-density lipoprotein cholesterol level of 181 mg/dL (4.68 mmol/L). Arterial blood gas showed metabolic acidosis with the following values: pH, 7.18; P_{CO_2}, 14 mm Hg; bicarbonate, 5.4 mEq/L (5.4 mmol/L); and base excess, −23 mEq/L. Simultaneous urinary pH was 7.1. Serum sodium level was 145 mEq/L (145 mmol/L), potassium level was 2.4 mEq/L (2.4 mmol/L), chloride level was 102 mEq/L (102 mmol/L), lactate level was 36 mg/dL (4 mEq/L), ammonia level was 117 mg/dL (69 μmol/L), and anion gap was 36 mEq/L (36 mmol/L). An abdominal ultrasound showed bilaterally enlarged kidneys with medullary nephrocalcinosis (right, 5.97 × 2.77 cm; left, 5.82 × 2.81 cm; Fig 1). The liver and spleen were normal on ultrasonography.

Additional Investigations

Although the child did not have hypoglycemia at admission, blood glucose levels after 90 and 120 minutes of the last feed were 50 mg/dL (2.78 mmol/L) and 45 mg/dL (2.50 mmol/L), respectively. Urinary spot calcium-creatinine ratios were performed, which showed high-normal values for the age of 0.76 and 0.82 mg/mg on 2 separate occasions. Urinary spot albumin-creatinine ratio was 50 mg/g. Urine aminoacidogram did not show an abnormal pattern; urinary proteins and glucose were negative; ferric chloride (for phenylketonuria and organic acidurias), sodium cyanide nitroprusside (for homocystinuria), and dinitrophenylhydrazine (for phenylketonuria and organic acidurias) test results were also negative. After bicarbonate loading, the urinary/blood P_{CO_2} difference was 5 mm Hg, indicating the presence of distal renal tubular acidosis. A glucose tolerance test (administration of 1.75 g/kg of glucose orally) was performed and showed glucose values at baseline and 30, 60, and 90 minutes of 64 mg/dL (3.55 mmol/L), 134 mg/dL (7.44 mmol/L), 85 mg/dL (4.72 mmol/L), and 50 mg/dL (2.78 mmol/L), respectively. The corresponding values for lactate at these times were 43.7 mg/dL (4.9 mEq/L), 21.4 mg/dL (2.4 mEq/L), 8.5 mg/dL (0.9 mEq/L), and 4.8 mg/dL (0.5 mEq/L), respectively.

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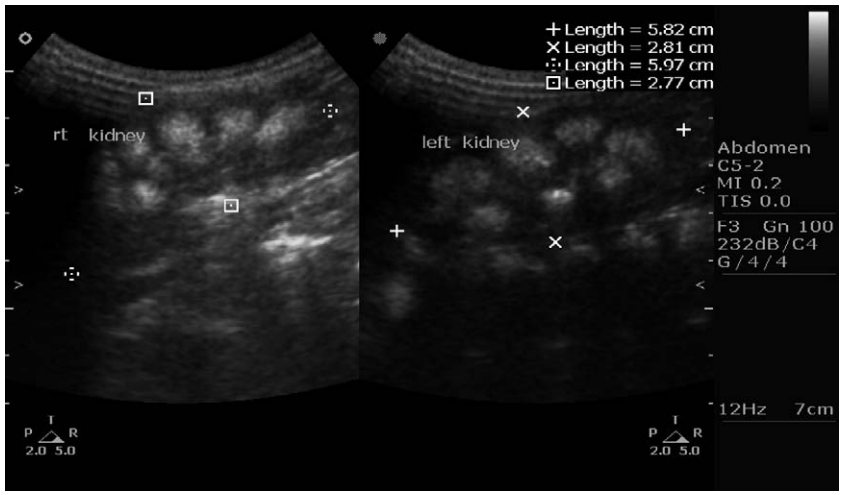

Figure 1. Renal ultrasound of the child shows bilateral medullary nephrocalcinosis.

After stabilization of the patient, a liver biopsy was performed that showed mildly enlarged hepatocytes with homogeneous cytoplasm and compressed central nuclear sinusoids. The liver biopsy specimen (light microscopy) was interpreted as compatible with glycogen storage disease. Facilities for enzymatic assay of the biopsy were not available. The genomic DNA of the patient was tested for the mutation most commonly seen by our local genetic testing facility in cases of glycogen storage disorder Ia. In brief, the glucose-6-phosphatase gene (*G6PC*; found at 17q21 locus) was assayed by means of mutation-specific polymerase chain reaction of DNA derived from peripheral-blood leukocytes. The mutation, which affects codons 49 and 50, was not detected in this patient, and complete gene sequencing for identification of other sequence variants was not feasible because of limited resources.

Diagnosis

Most patients with glycogen storage disorder type I have a deficiency of the enzyme glucose-6-phosphatase, but the condition also can occur in a small number of patients because of deficiency of a translocase that transports glucose-6-phosphatase across the microsomal membrane for its final action. Presence of a previously characterized mutation in the *G6PC* gene or the translocase gene (*TIMM8B;* 11q23 locus) is confirmatory of the disorder and further evaluation (enzymatic assay, glucose tolerance test) is not required in these patients.[1] However, in this patient, only limited genetic testing could be done; therefore, a glucose tolerance test was performed. During 2 hours after administration of oral glucose (1.75 g/kg), there was a consistent decrease in lactate levels, as noted. This suppression of lactate with an increase in blood glucose levels is characteristic of glycogen storage disease type I.[1] After these investigations, a final diagnosis of glycogen storage disease type I was made.

Clinical Follow-up

The child was started on a dietary regimen of frequent feeds (every 2 hours), and precooked cornstarch (1.6 g/kg) was added to a few feeds, especially the nocturnal ones. Her parents were also advised to give her plenty of water. The child was started on potassium citrate supplements along with iron (3 mg/kg/d) and multivitamin supplements according to recommended dietary allowances. These interventions were followed by a symptomatic improvement in the child. At the last follow-up at 18 months of age, the symptoms of polydipsia and polyuria were relieved and weight had increased to 7.7 kg (<3rd centile), and length, to 73 cm (<3rd centile), although failure to thrive persisted. The biochemical profile also showed improvement (Table 1). Acidosis improved and hypercalciuria decreased.

DISCUSSION

This infant on repeated evaluation had metabolic acidosis. The serum anion gap $[Na^+] - ([Cl^-] + [HCO_3^-])$, normally 12 ± 4 mEq/L (12 ± 4 mmol/L), was grossly increased at 36 mEq/L (36 mmol/L). Thus, the increased lactate level of 4 mEq/L in this patient clearly was not sufficient

Table 1. Biochemical Parameters at Presentation and Follow-up

Investigations	At Initial Evaluation	At Last Follow-up (18 mo)
Blood gas pH	7.18	7.34
Bicarbonate (mEq/L)	5.4	19.8
Serum triglycerides (mg/dL)	996	341
Serum cholesterol (mg/dL)	239	184
Serum creatinine (mg/dL)	0.7	0.5
Urinary calcium-creatinine ratio (mg/mg)	0.82	0.2

Note: Serum creatinine in mg/dL may be converted to μmol/L by multiplying by 88.4; triglycerides in mg/dL to mmol/L by multiplying by 0.01129; serum cholesterol to mmol/L by multiplying by 0.02586.