An 18-Month-Old Boy with Diarrhea and an Elevated Biochemical Parameter

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An 18-month-old boy presented to his primary care pediatrician with a complaint of diarrhea for the past 5 days. The diarrhea was frequent, watery, but without mucus or blood. The diarrhea was not associated with vomiting, fever, cough, or skin rash. His past medical history is significant only for mild asthma, and his immunizations are up-to-date.

The physical examination revealed an alert, well-developed boy with a weight of 11.9 kg (54th percentile), height of 84.5 cm (77th percentile), and normal vital signs. His abdomen was soft, nontender, and without hepatosplenomegaly or signs of dehydration. The rest of the physical examination was normal.

A clinical diagnosis of viral gastroenteritis was made and oral rehydration therapy and dietary modifications were recommended. After 3 days he returned to the clinic because of the persistence of the diarrhea, and there were still no other symptoms. Once again, the results of his physical examination were normal. Because of the continuation of the diarrhea, laboratory tests (blood, urine, and stool) were performed, and the results were as follows: hemoglobin, 11.5 g/dL; white blood cells, 9.2 10^3/μL; platelets, 367 10^3/μL (with a normal differential count); C-reactive protein, <0.5 mg/dL; glucose, 75 mg/dL; urea, 25 mg/dL; creatinine, 0.20 mg/dL; potassium, 4.3 nmol/L; sodium, 138 nmol/L; protein, 6.2 g/dL; albumin, 4.1 g/dL; bilirubin, 0.20 mg/dL; ferritin, 20 ng/mL; aspartate aminotransferase, 37 U/L; alanine aminotransferase, 26 U/L; gamma-glutamyl transpeptidase, 5 U/L; calcium, 9.3 mg/dL; and phosphorus, 4.9 mg/dL. Urinalysis was normal, and stool for culture, ova, parasites, Giardia lamblia antigen, rotavirus, and adenovirus was negative. Blood serology was negative for Epstein-Barr virus (EBV), hepatitis C, and for immunoglobulin M cytomegalovirus (CMV) antibodies, and positive for immunoglobulin G CMV antibodies, indicating a past infection with CMV.

An elevated biochemical parameter in the blood revealed a condition that may be associated with the clinical presentation (gastroenteritis) described, appearing mainly in infancy and early childhood.

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Editor’s note: Each month, this department features a discussion of an unusual diagnosis. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via email at pedann@Healio.com.
BTH of infancy and early childhood is a situation of transient and marked elevation of serum ALP in infants and toddlers of both sexes without any evidence of bone or liver disease. BTH is not sufficiently recognized or even suspected by most primary care pediatricians because textbooks either do not mention it or discuss it only briefly. The diagnosis and documentation of BTH can help avoid unnecessary and expensive laboratory tests.

The prevalence of BTH is estimated to be between 1.5% and 5.1% in infants and small children. Serum levels of ALP >1000 U/L (3 times the upper limit of normal) were documented in 2.8% of the children, most of them younger than age 2 years. Moderate elevations of serum ALP were found in 5.1% of the study participants.

Bach (1954) was the first to describe the condition, and Kraut et al. (1985) determined the 7-point criteria for diagnosing BTH (Table 1).

Despite the criteria shown in Table 1, there are studies describing patients older than age 5 years, and approximately 25% of published cases occurred in children age 37 months or older or in adults. The normalization period of the elevated serum ALP was more than 17 weeks in approximately 20% of the published cases.

Most children with BTH are healthy, and the condition often occurred in clinical situations such as gastroenteritis, respiratory infections, other viral infections with EBV, enteroviruses, HIV, failure to thrive, and asthma.

Approximately 13% of published pediatric cases of BTH occurred in patients with a pre-existing chronic disease such as leukemia, lymphoma, liver disease, rickets, and other metabolic osseous activity, and also in children who had undergone kidney or liver transplant. In such situations, the values of serum ALP are less elevated than those found in BTH, and may reflect a seasonal appearance of BTH in late summer and early fall had been described in some series. No complications were noticed up to 4 years after the initial episode of BTH.

### Differential Diagnosis

The differential diagnosis of an elevated serum ALP, especially the liver isoenzyme, is usually associated with clinical situations suggesting cholestaticis, intrinsic liver disease, malignancy with liver metastases, renal disease, and bowel diseases and conditions such as bowel perforation and infarction, inflammatory bowel disease, pancreatitis, and malabsorption.

The elevation of the bone isoenzyme of the serum ALP is mainly seen in cases of rickets, osteomalacia, and healing fracture.
Heightened awareness for rickets or vitamin D deficiency should be raised in young children with malabsorptive conditions, those treated with anticonvulsant and antiretroviral medications, those on vegetarian diets, children with dark skin, and in breast-fed infants who are not receiving vitamin D supplementation. Other conditions in which an elevated serum ALP can be seen are pregnancy, congestive heart failure, sarcoidosis, secondary hyperparathyroidism, EBV, CMV infections, and sepsis.

Pathogenesis

The pathogenesis is unclear because both liver and bone isoenzymes are elevated. The theory that predominates states that there is an excessive content of sialic acid in the isoenzymes, resulting in sialylation of ALP, which decreases the clearance of the isoenzymes and leads to hyperphosphatasemia.

Another hypothesis is that the increased ALP is due to catch-up growth by the child with insufficient vitamin D and weight loss at a rate that overcomes the normal desialylation of the enzyme. One can expect a clinical or subclinical vitamin D insufficiency with hyperphosphatasemia, but this hypothesis was contradicted by finding no difference in serum levels of vitamin D, parathyroid hormone, calcium, or phosphorus among healthy infants and children with BTH compared to those with normal serum levels of ALP.

CONCLUSION

BTH should be suspected in otherwise healthy infants and children with a marked elevation in serum ALP who are usually younger than age 5 years and present with a clinical situation such as failure to thrive, gastroenteritis, asthma, and other viral infections with (usually) a normal physical examination and without any clinical evidence of liver or bone disease.

Approximately 13% of cases with transient elevations of serum ALP appear in people with a chronic disease, but the ALP values are usually less elevated than those found in healthy people with BTH. Approximately 25% of the individuals with BTH may be older than age 5 years, and in 20% the normalization period is longer than 4 months.

The mechanism of serum ALP elevation seems to be a reduced clearance from the circulation by excessive sialylation rather than a transient increased release of the enzyme.

The benign nature of the condition should be explained to the parents with the expectation of a normalization of serum ALP in about 4 months.

REFERENCES