Benign Transient Hyperphosphatasemia

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A 13-month-old girl presented to our clinic for a routine check-up. She was developing typically for her age but was noted to have decreasing growth velocity.

HISTORY

She was a product of an uncomplicated pregnancy and born at full term. She was exclusively breastfed with vitamin D supplementation until 6 months of age when her parents began introducing complementary foods. At 8 months of age, her mother had experienced decreased breastmilk supply and, therefore, started to introduce formula in addition to providing expressed breastmilk.

By 10 months of age, the patient was consuming formula and table foods only. Her weight trajectory had decreased from the 33rd percentile at 6 months of age to the 4.5th percentile at 10 months of age, using the Centers for Disease Control and Prevention (CDC) clinical growth chart. The patient's parents offered her a wide variety of table foods and elected to give European cow's milk–based formula to provide liquid nutrition.

Results of laboratory tests at the patient's 10-month visit revealed a low level of hemoglobin at 10.3 g/dL (reference range, 11.3-14.1 g/dL). A presumptive diagnosis of iron deficiency was made at that time. Supplemental iron was prescribed, and dietary education was provided to the patient's parents.

PHYSICAL EXAMINATION

At her 13-month check-in, the patient's weight had dropped to the 1.3rd percentile, with associated stunting of length trajectory (53rd percentile decreased to 11th percentile on the CDC chart). She did not have diarrhea, bloating, flatulence, skin changes, vomiting, fever, fatigue, or other systemic signs.

DIAGNOSTIC TESTING

Results of laboratory tests showed an elevated alkaline phosphatase level of 6741 U/L (reference range, 122-469 U/L), a normal vitamin D level of 53.9 ng/mL (reference range, 30-100 ng/mL), a normal parathyroid hormone (PTH) level of 23.9 pg/mL (reference range, 10-65 pg/mL), and a normal hemoglobin level of 12 g/dL on iron supplementation. Additional testing included a celiac panel, thyroid function tests, a complete blood count, a basic metabolic panel, liver function tests, and a bilirubin test. Results were all unremarkable.

A skeletal survey was negative for metabolic bone disease or fracture. A referral to endocrinology was made with consideration of broad differential. In addition, the patient was started on nutritional supplementation for failure to thrive.

Results of repeat tests conducted 2 weeks later showed a decreased alkaline phosphatase level at 1636 U/L. Six weeks later, results had normalized to 196 U/L. During this same period of improvement in her laboratory findings, her growth trajectory improved with cow's milk–based nutritional supplement twice daily. Her weight trajectory increased to the 2.75th percentile, and her length increased to the 20th percentile.

A diagnosis of transient hyperphosphatasemia of childhood was made, which was noted to occur with failure to thrive from presumed inadequate nutritional intake. She continued to develop appropriately.

DISCUSSION

Transient hyperphosphatasemia is characterized by a benign significant elevation in alkaline phosphatase levels typically noted in children aged 6 to 24 months.[1,2] Prevalence of benign transient hyperphosphatasemia is thought to be approximately 2.8% to 6%, with alkaline

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phosphatase levels greater than 1000 U/L.[1,2] A diagnosis of transient hyperphosphatasemia can be made if the alkaline phosphatase level returns to within normal values for age within about 4 months following repeat laboratory testing.

Of note, transient hyperphosphatasemia does not appear to be linked to anthropometric measures, vitamin D status, PTH level, or serum calcium and phosphate levels based on recent literature.[1,3,4] Other recent reports[5] suggest a possible association in patients with gastroenteritis, respiratory infection, asthma, and failure to thrive. These associations may be secondary to increased laboratory evaluations in these patients.

Elevated alkaline phosphatase levels can also be present in conditions that require treatment, including liver disease, bone disease, and oncologic processes. Pediatricians must carefully assess for underlying conditions that will require treatment while avoiding unnecessary tests in infants and children. Appropriate awareness of this diagnosis and other possible diagnoses for elevated alkaline phosphatase can help prevent excess laboratory testing and use of resources. Evaluation should begin with clinical assessment and laboratory assessment.[3]

The clinician must first evaluate the patient's history, specifically assessing for risk factors such as bone, liver, kidney, and systemic disease that may lead to elevated alkaline phosphatase.[4] Medications should also be reviewed with special attention to antiepileptic medications, since they may cause an elevation in alkaline phosphatase.[6] Clinicians should also assess risk factors for nutritional rickets and underlying bone disease by asking about vitamin D supplementation, exposure to sunlight, prematurity, fracture history, and bone pain. Symptoms suggestive of liver disease such as jaundice, scleral icterus, dark-colored urine, and right upper-quadrant pain should be assessed.[3] The patient history must include symptoms that may indicate systemic illnesses such as poor growth, lethargy, weight loss, fever, and anorexia.

Physical examination of these patients should evaluate for bone deformities—including beading at the costochondral junction, delayed closure of fontanelles, flaring of the wrist or ankle metaphases, and bowing of long bones—as well as signs of liver disease such as hepatomegaly, scleral icterus, and jaundice. Laboratory evaluation may include serum aminotransferase, alanine aminotransferase, total and direct bilirubin, Ɣ-glutamyl transpeptidase, calcium, phosphorus, 25-hydroxyvitamin D (calcidiol), PTH, blood urea nitrogen, and creatinine to screen for possible liver disease, rickets, and renal disease. Although a fractionated alkaline phosphatase is sometimes used to delineate the origin from bone, liver, or intestines, it is often not necessary for initial evaluation.

While patients with transient hyperphosphatasemia typically do not have alkaline phosphatase levels that exceed 2000 U/L, elevated levels beyond 3 to 4 times the upper limit of normal for age does not rule out benign transient hyperphosphatasemia. In patients with a significant elevation of alkaline phosphatase, benign transient hyperphosphatasemia must still be considered as a possible etiology, although conditions requiring further treatment must be ruled out.

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