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LETTER TO THE EDITOR

Benign familial hyperphosphatasemia: A little-known entity

Hiperfosfatasemia familiar benigna. Una entidad poco conocida

To the Editor,

Alkaline phosphatase (ALP) encompasses a group of enzymes that catalyze the hydrolysis of multiple esters at an optimal alkaline pH.[1] Increased ALP derives from tissues whose metabolism is functionally altered (biliary obstruction) or overstimulated (placenta in the third month of pregnancy and during growth). The serum activity of ALP primarily comes from 3 sources (liver, bone, and GI tract), and under normal conditions, the first 2 account for almost 90% of its levels in equal proportion. The physiological function of ALP depends on the origin: in the liver, it participates in the transport of choline across the canalicular membrane of hepatocytes and biliary epithelial cells, while at bone level, it is involved in the processes of phosphate hydrolysis, transport, and deposition of hydroxyapatite, favoring the mineralization of the bone matrix. The intestinal isoform of ALP is the least present in the plasma of healthy individuals, with its increase being described in children with intestinal conditions and patients with severe liver diseases.[2] There is a benign familial form of increased intestinal ALP, especially in individuals with blood groups B and O, known as benign familial hyperphosphatasemia.

This is the case of a 53-year-old woman with no relevant personal history with isolated and persistently elevated ALP detected in a routine analysis, in the absence of hepatobiliary or bone disease. An intestinal origin was identified as being above normal levels, as well as in a first-degree relative, confirming the diagnosis of benign familial hyperphosphatasemia.

The patient had no relevant medical-surgical history, no smoking or alcohol consumption, or drug use. She was referred for persistent ALP elevation of 3–3.5 times the upper limit of normal (ULN) detected 10 years prior. Upon anamnesis, there were no constitutional or GI symptoms, itching, or bone pain. She also did not report a history of bone fractures, dental problems, or use of herbal products. Physical examination revealed vital signs within normal limits, without jaundice or signs of chronic liver disease. Both cardiovascular and lower limb examinations were normal. Abdominal examination revealed no signs of ascites, organomegaly, or venous collateral circulation. As part of the study, the following analytical determinations were performed: complete blood count and biochemistry showed ALP levels at 345 UI/L (reference range 40–129 IU/L), without any changes to gamma-glutamyltransferase (GGT), transaminases, or bilirubin; calcium-phosphorus metabolism (serum calcium and phosphorus, parathyroid hormone, 25-hydroxyvitamin D, formation markers [osteocalcin and C-terminal propeptide], C-terminal type I collagen and bone resorption [C-terminal telopeptide], beta [Crosslaps] of type I collagen, all within normal range); proteinogram, immunoglobulins, beta-2 microglobulin, erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), extractable nuclear antigen (ENA), antimitochondrial antibodies (AMA), and type 1 liver and kidney microsomal antibodies (anti-LKM1), all within normal range or negative. Imaging modalities were also performed: X-ray of the cervicodorsolumbar spine (without any changes being reported), whole-body bone scintigraphy with technetium-99m sodium oxydronate (99mTc-HDP) (without pathological uptake), and abdominal ultrasound with no signs of hepatobiliary disease. After excluding bone and hepatobiliary disease as causes of hyperphosphatasemia, an alternative origin was considered, and the determination of ALP isoenzymes was requested, showing an increase in the intestinal form: hepatic origin, 34%; bone, 25%; and intestinal, 41% (normal values up to 14%). Furthermore, the blood type was determined (O). Looking into the family history, the patient said that her 63-year-old brother also exhibited these analytical changes since youth. A sustained elevation of 5–6 times the ULN of ALP was confirmed, thus, like the index case, the study was completed with normality in all supplementardy tests. The determination of ALP isoenzymes also showed an increased intestinal fraction (66%). The study results confirmed the diagnosis of benign familial hyperphosphatasemia in both siblings.

In the presence of elevated ALP, its extraction should initially be confirmed in fasting to avoid any transient elevations. Once the alteration has been confirmed, the levels of transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), GGT, or 5'-nucleotidase, and total bilirubin should be evaluated, as the simultaneous elevation of any of these parameters would suggest hepatobiliary causes. In the case of isolated elevation, the study should be completed with calcium-phosphorus

metabolism (calcium, phosphorus, parathyroid hormone, 25-hydroxyvitamin D, formation markers, and bone resorption) to rule out a bone origin such as in cases of bone metastases, Paget's disease, primary hyperparathyroidism, osteomalacia, or renal osteodystrophy. Other causes that should be considered include thyroid alterations, paraneoplastic origin, and macro-ALP. Performing electrophoresis allows for the identification of isoenzymes or fractions of ALP and localizes the tissue from which serum ALP originates, thereby guiding the study.

Benign familial hyperphosphatasemia is a rare biochemical anomaly characterized by the presence of persistently elevated serum ALP levels in several members of the same family in the absence of a known disease or cause of hyperphosphatasemia. It is a benign condition that does not translate into skeletal alterations that has been described as having an autosomal dominant inheritance.[3] Four different genes that code for the different isoenzymes of ALP have been identified: the genes for the liver, bone, and kidney isoenzymes are located on chromosome 1, while the genes for the intestinal and placental isoenzymes are located on chromosome 2.[4] The reasons for this plasmatic increase are currently unknown. In cases described in the literature, the diagnosis was achieved incidentally during routine analysis, although in several cases the reason for the study was the presence of joint pain. In conclusion, this benign entity should be known, and in cases of persistent isolated ALP elevation without bone or hepatobiliary disease, isoenzymes should be determined to clarify its origin.[5] An increase in the intestinal fraction would suggest this entity, warranting inquiry into the family history for confirmation to avoid any invasive and unnecessary tests from being performed in these patients.

Ethical disclosures

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Declaration of competing interest

None declared.

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Antonio Bustos-Merlo*, Antonio Rosales-Castillo

Secretaría de Medicina Interna, Hospital Universitario Virgen de las Nieves, Granada, Spain

* Corresponding author.
E-mail address: antoniobustosmerlo@gmail.com
(A. Bustos-Merlo).