

Marked Transient Alkaline Phosphatemia Following Pediatric Liver Transplantation

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• An isolated marked transient rise in serum alkaline phosphatase levels in otherwise healthy children is a well-documented occurrence. However, in children undergoing liver transplantation, elevated alkaline phosphatase values raise the possibility of biliary obstruction, rejection, or both. During a 6-year period, 6 of 278 children undergoing liver transplantation exhibited a similar phenomenon as an isolated abnormality. None had rejection, biliary obstruction, or other allograft dysfunction during a long follow-up. Eventually and without intervention, the alkaline phosphatase levels returned to normal. These instructive cases suggest that caution be used in advocating invasive procedures if elevated alkaline phosphatase levels are an isolated abnormality, and close observation with noninvasive testing is recommended.

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After orthotopic liver transplantation, liver function test results are serially determined to monitor allograft function. Serum alkaline phosphatase (AP) and γ -glutamyltransferase (GGT) levels, when markedly elevated, lead to a strong suspicion of either allograft rejection or biliary obstruction. Further investigations, sometimes invasive, are often required to elucidate the exact problem.

An isolated, transient, marked elevation of serum AP levels without any evidence of biliary obstruction has been

reported in infants and children who have not undergone transplantation.¹⁻⁷ Infusions of serum albumin⁸ and therapy with sulfamethoxazole-trimethoprim⁹ have been reported to cause elevation of AP levels, but the cause in most patients is unknown. We have encountered six children who had an isolated, transient, marked elevation of serum AP levels at varying intervals following liver transplantation without evidence of biliary obstruction or rejection. The intent of this article is to bring this problem to the attention of physicians caring for pediatric liver transplant recipients and to urge caution in advocating invasive procedures.

PATIENTS AND METHODS

During the years 1981 through 1986, 278 children received 378 liver transplants in the University of Pittsburgh (Pa) Children's Hospital transplant program.

Part of the postoperative follow-up after discharge consisted of periodic checks of body weight, a complete blood cell count, and determinations of prothrombin and partial thromboplastin times, serum total bilirubin, alanine and aspartate aminotransferases, AP, GGT, calcium, and phosphorus. In that 6-year period, six children exhibited a

marked transient rise (>1500 U/L) in serum AP levels in the posttransplant period, with other liver function study results, including the GGT determination, being normal. Whenever an isolated elevation of serum AP levels was encountered, an abdominal ultrasound was performed for evidence of intrahepatic biliary ductal dilatation. Skeletal roentgenograms were obtained for all six children, and a serum AP isoenzyme fractionation was performed in four of six children with elevations in serum AP levels.

The age range of children presenting with transient elevations of serum AP levels was 2 to 6 years, with an average age of 38 months. The clinical details of these children are given in the Table. Five had biliary atresia and one had α_1 -antitrypsin deficiency. As a rule, the transient elevation in serum AP levels occurred following discharge from the hospital. The time interval between transplantation and the rise in AP levels varied between 3½ to 14 months. There were no major alterations in the list of drugs these patients were receiving before the rise in AP levels. With ultrasound, none of the children had evidence of biliary ductal dilatation suggestive of obstruction. The bilirubin, alanine aminotransferase, aspartate aminotransferase, and GGT values remained normal. A liver biopsy or cholangiogram during or after the period of rise in serum AP values was not performed. Of the four children in whom iso-

Clinical Details of Six Patients With Transient Elevation of Serum AP Levels*

Patient No./Age, y/Sex	Time Interval From Transplant, mo	Highest AP Level, U/L	Predominant Isoenzyme Fraction	Duration of AP Elevation	Follow-up After Normalization of AP, mo
1/6/M	12	2500	Not done	4 wk	54
2/3/M	12	4095	Not done	4 wk	50
3/2½/M	12	1737	Bone	2 wk	30
4/2½/F	14	4651	Liver	10 wk	26
5/3½/F	3½	8680	Bone	8 wk	28
6/2/F	5	4550	Bone	16 mo	9

*AP indicates alkaline phosphatase.

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enzyme fractionation data were available, three showed an increased bone fraction. The fourth child showed an increase in the liver fraction of serum AP. Of the six children, five had long-bone roentgenograms that did not support a diagnosis of rickets (the sixth patient had a skeletal survey at the time of transplant that gave normal results). The duration in which the AP levels remained elevated ranged from 2 weeks to 16 months. In the follow-up period after normalization of the serum AP values (9 to 54 months), none of the children exhibited any features of obstruction or rejection. All the children improved without having to undergo any surgical procedures. All six children are alive and doing well, with normal allograft function.

COMMENT

In 1954, Bach¹ first reported the occurrence of an isolated marked transient elevation of serum AP levels in three infants. About 1.5% of 500 serum samples from healthy children had marked elevation of serum AP levels in a study conducted by Asanti et al² in 1966. In our follow-up of children who had received liver transplants, the incidence of isolated marked transient elevations of AP levels was 2.1%. Isoenzyme fractionation studies of cases reported in the literature have revealed the source of this elevated enzyme level to be bone, liver, or both.^{3,7} In four of our patients in whom isoenzyme fractionation data were obtained, bone fraction was predominant in three patients and liver fraction in one patient. It is not

known why a marked rise suddenly occurred in the serum level of this enzyme, as previously reported in the healthy children and now in the transplant recipients.

Confronted with the elevation of serum AP levels after liver transplantation, the clinician is prompted to consider the pathologic conditions of the liver, skeleton, or both. Paramount among these considerations are biliary obstruction and allograft rejection. Biliary obstruction can often be detected by the noninvasive means of ultrasound. Utilization of more invasive methods, including percutaneous transhepatic cholangiography or surgery, should only be considered if the ultrasonogram reveals obstruction, or continued clinical or laboratory follow-up reveals additional evidence supportive of biliary obstruction. Rejection often presents as an elevation of the canalicular enzyme levels, including the serum AP levels, before a significant rise in transaminase levels. A rise in GGT levels in allograft rejection mimics the elevation in serum AP levels. The isolated nature of the elevation of serum AP levels in our patients was reassuring and allowed us to avoid performing an allograft biopsy in favor of close clinical or laboratory follow-up. Subsequently, long-term follow-up of these children has supported this conservative approach, since none have shown evidence of either obstruction or rejection.

Other considerations as causative for the isolated elevation of serum AP levels include bone reactivity, infusion of serum albumin,⁸ and sulfamethoxazole-trimethoprim therapy.⁹ While rapid correction of rickets after liver transplantation is a well-known occurrence, none of our patients had rickets, as determined by use of roentgenography. The possibility of subclinical rickets, however, still exists. Also, none of the children demonstrated a rapid growth spurt beginning at the time of the rise in serum AP levels. None of our patients were receiving albumin infusions at the time of the rise in serum AP levels, and only one patient was receiving sulfamethoxazole-trimethoprim.

In line with reports in the literature,^{1,7} in all of our patients, elevated serum AP values ultimately returned to normal without medical or surgical intervention. When physicians caring for children who have received liver transplants are confronted with elevated serum AP levels but normal liver transaminase, GGT, and bilirubin levels and a normal ultrasonogram, they should choose close observation and frequent laboratory follow-up as the most prudent medical course.

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