Transient Hyperphosphatasemia of Infancy—an Insufficiently Recognized Syndrome

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Spectacular transient increases in serum alkaline phosphatase were observed in five infants in the absence of demonstrable pathology.

Serum alkaline phosphatase activity is above normal in several clinical conditions (1, 2). Spectacular values are almost invariably associated with overt disorders of the skeleton or the hepatobiliary system or with the administration of alkaline phosphatase in intravenous solutions (3, 4).

In this paper we report five infants with serum alkaline phosphatase activities greater than 20-fold the upper limit of the range for normal adults. The associated symptoms showed no consistent pattern from patient to patient and could not be logically related to the increase in serum alkaline phosphatase activity.

Case Report

J.H. (RAHC 265765) was admitted to hospital at the age of seven months because of intermittent vomiting, dating from the time of birth, and “poor weight gain.” Physical examination showed no abnormality. The height and weight of the child were in the center of the normal range. Results of skeletal roentgenograms and a complete blood-cell count were within normal limits. Skeletal scintiscans were not done. Results of chemical tests [including serum calcium, serum inorganic phos-

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months to two years of age, and none showed any clinical evidence of hepatic or skeletal disease. Except in Case 1 (see Table 1) there was no history of drug ingestion or intravenous therapy. Skeletal roentgenograms were normal in each instance. All the patients showed spectacularly high values for serum alkaline phosphatase, but other biochemical variables measured were within normal limits.

In each of the five patients described in this paper, studies of isoenzymes suggested that the enzyme originated in the skeletal system. Values had become normal within eight weeks in all patients. None of the infants described in this paper developed any further symptoms or showed any abnormally high serum alkaline phosphatase values during the period of follow up (six months to two years). The authors of the earlier publications presented no follow-up data.

We have no information concerning the pathogenesis of this condition, which we have chosen to call "transient hyperphosphatasemia of infancy."

There was no evidence for the presence of any skeletal disorder that might have caused an increase in serum alkaline phosphatase of this magnitude. Isolated transient hyperphosphatasemia has been described in patients with pulmonary emboli (14), but the changes have always been of a relatively minor nature. Certain nutritional stimuli are known to cause a marked increase in serum alkaline phosphatase activity in experimental animals (15) and particularly in the neonates of some species (16, 17). Such changes have been shown to be the result of entry of intestinal alkaline phosphatase into the circulation (15, 17), whereas in our patients all the evidence points to the skeleton as the tissue of origin (Table 1). Viral disorders have been described in the mouse that are characterized by an increase in certain circulating enzymes (18). To our knowledge, no such disorders have been described for skeletal alkaline phosphatase in man.

Table 1. Clinical Data on the Subjects

<table>
<thead>
<tr>
<th>Initials</th>
<th>Age (months)</th>
<th>Sex</th>
<th>Clinical features</th>
<th>Highest serum alkaline phosphatase</th>
<th>Tissue origin as determined by isoenzymic studies</th>
<th>Time until normal value recorded (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. C.D.</td>
<td>18</td>
<td>F</td>
<td>Irritable behavior. Had received pipenzolate bromide, promezatamide hydrochloride, and dicloxyline intermittently. Urinary catechola- mines transiently increased.</td>
<td>540 K.A.</td>
<td>Bone</td>
<td>6</td>
</tr>
<tr>
<td>3. J.H.</td>
<td>7</td>
<td>F</td>
<td>Feeding problem. See case report.</td>
<td>2410 U</td>
<td>Bone</td>
<td>7</td>
</tr>
<tr>
<td>4. N.L.</td>
<td>5</td>
<td>F</td>
<td>Fits. Mental retardation. No anticonvulsants.</td>
<td>350 K.A.</td>
<td>Bone</td>
<td>7</td>
</tr>
<tr>
<td>5. D.B.</td>
<td>9</td>
<td>M</td>
<td>Failure to thrive. Lowest 3rd percentile height and weight.</td>
<td>6300 U</td>
<td>Bone</td>
<td>5</td>
</tr>
</tbody>
</table>

a Heat inactivation (6) in Cases 3–5 and both heat inactivation and electrophoresis (6) in Cases 1 and 2.

b K.A. = King–Armstrong units/100 ml [method of Kind and King (6)]; U = international (IUB) units/liter [method of Morgenstern et al. (5)].

Table 2. Features of Transient Hyperphosphatasemia of Infancy

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Bach (10)</th>
<th>Asanti et al. (11)</th>
<th>This paper</th>
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<tbody>
<tr>
<td>(n = 3)</td>
<td></td>
<td></td>
<td>(n = 5)</td>
</tr>
<tr>
<td>2–18</td>
<td>2–15</td>
<td>5–18</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Not stated</td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>Presentation</td>
<td>&quot;Normal control&quot;</td>
<td>&quot;Normal control&quot;</td>
<td></td>
</tr>
<tr>
<td>Method of assay</td>
<td>Huggins and Talalay (12)</td>
<td>Bessey et al. (13)</td>
<td>See Table 1</td>
</tr>
<tr>
<td>Degree of elevation</td>
<td>Up to 18 X U.L.</td>
<td>11–23 X U.L.</td>
<td>See Table 1</td>
</tr>
<tr>
<td>Duration of biochemical abnormality (weeks)</td>
<td>6–8</td>
<td>6–12</td>
<td>5–7</td>
</tr>
<tr>
<td>Other biochemical determinations</td>
<td>Not stated</td>
<td>Aspartate aminotransferase normal</td>
<td>All normalc</td>
</tr>
</tbody>
</table>

a As reported in three publications.

b U.L. = upper limit of the reported normal adult range for the method used.

c Aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, bilirubin, calcium, phosphate.
It has been suggested that Paget's disease is due to a slow virus (19). If this is the case, it is conceivable that it may have its genesis during a relatively asymptomatic period in infancy and that we chanced to examine these infants at the time of their original infection. This suggestion is obviously speculative at this stage and could only be substantiated or refuted by long-term follow-up studies.

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References