Transient Hyperphosphatasemia in a Child with Autosomal Recessive Vitamin D Dependency

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The case of a 4.5-year-old girl with autosomal recessive vitamin D dependency is described. Although she had been effectively treated since one month postpartum with 1α-hydroxycholecalciferol [1α(OH)D₃, alfalcacidol], her mean alkaline phosphatase (EC 3.1.3.1) activity in serum increased to 3680 U/L from a stable value [335 (SD 50) U/L; n = 12] within three weeks, then returned to baseline over the ensuing four months. Transient hyperphosphatasemia was diagnosed. Extensive investigation of an isolated episodic increase in alkaline phosphatase activity is as superfluous in the child with adequately treated metabolic bone disease as it is in other healthy and asymptomatic children.

Additional Keyphrases: alkaline phosphatase · heritable disorders · vitamin D-dependent rickets · pediatric chemistry

Transient hyperphosphatasia can be a benign and asymptomatic biochemical event that affects a small, select group of infants and young children (1-3). It is usually discovered serendipitously during routine investigations for other unrelated conditions, but it can be the source of a needless and usually unrewarding search for an underlying ailment.

Here I report its occurrence in a child with autosomal recessive vitamin D dependency and present data documenting undisturbed mineral metabolism for a considerable interval before and after the acute event.

Methods

This 4.5-year-old girl, like all patients with inherited rickets who are seen in our clinic, was monitored routinely to optimize therapy. The urinary calcium/creatinine ratio, and serum calcium, phosphorus, and alkaline phosphatase (EC 3.1.3.1) activity were measured monthly. The patient was seen at six-month intervals to measure growth and review therapy. 25-Hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [1,25(OH)₂D] were measured in serum. Serum parathyrin was measured by radioimmunoassay, with antibody primarily directed at the N-terminal region.

Case Report

The parents of the proband were not known to be related, but they shared common surnames among their ancestors and resided in a restricted geographical area with a high prevalence of autosomal recessive vitamin D dependency. Their first child had been diagnosed with this disorder at age 14 months and was receiving effective therapy. The proband, born two years later, was entirely normal at birth. Her cord blood 25(OH)D concentration was 11 μg/L (reference interval: 14–38) and her 1,25(OH)₂D was 32 ng/L (reference interval: 28–58). When the infant was re-evaluated after one month, the serum calcium concentration was 2.43 mmol/L, serum phosphorus 1.29 mmol/L, serum 25(OH)D 45 μg/L, and 1,25(OH)₂D 6.7 ng/L. The parathyrin concentration in serum was 610 ng/L (normal, <360) and there was generalized aminoaciduria. A diagnosis of vitamin D-dependent rickets was made (4) and she was given 0.5 μg of alfalcacidol (1α-hydroxycholecalciferol) each day.

She progressed well and in 1984 was considered to be well-controlled with good radiographic results. Her height has been maintained at the 10th to 25th percentile for her cohort throughout.

During a routine clinic visit in May 1985 at age 53
months, she was observed to be healthy and in no distress. However, the laboratory reported that the serum alkaline phosphatase activity was 3680 U/L, some ninefold higher than the usual result for her [mean 335 (SD 50) U/L, n = 12; normal value <285]. A careful review of the records revealed no significant changes in serum calcium or phosphorous concentrations or in the urinary calcium/creatinine ratio over the previous 16 months (Figure 1). The dose of alfalcacidol had been unchanged (0.75 mg/day) for the previous 8.5 months, and a careful comparison of anteroposterior radiographic views of the knees and wrists with those taken six months earlier showed no sign of active rickets and no change in the pattern of mineralization. The parents noted that the patient had experienced mild flu-like symptoms with diarrhea three to four weeks earlier. However, there was no nausea or vomiting nor was the child kept home from pre-school classes.

Her alkaline phosphatase activity in serum decreased by nearly half, to 2000 U/L, two weeks later and was within the usual range of 300 to 400 U/L within three months. Because of the relatively high urinary calcium/creatinine ratios and the uncertainty of the origin of the massive increase in alkaline phosphatase, the alfalcacidol dose was reduced from 0.75 to 0.50 mg/day. Biochemical indices improved somewhat over the next six months, but there were no other clinical findings of note, and a subsequent review six months later was entirely unremarkable.

Discussion

Within the past few years, there has been a growing interest in the origin(s) of transient hyperphosphatasemia (1–3). Historically viewed as a minor curiosity, it is now recognized as a significant problem because of the amount of investigational effort that may be brought to bear on an ostensibly healthy child. Called the "Ulysses syndrome" by one group because of the long searches needed to convince the investigator that it is of no clinical consequence (5), transient hyperphosphatasia is a disorder of unknown etiology. The increased enzyme activity itself apparently results from release of increased amounts of isoenzyme from both liver and bone into the circulation (3), but other indices of mineral metabolism, including serum osteocalcin (6), remain entirely normal throughout the episode. This patient presented the rare opportunity for a review of biochemical indices of mineral metabolism for months before the event; there were no warning signs and no significant prodromal changes in these indices whatsoever. Concern as to the source of the increased alkaline phosphatase activity was naturally exacerbated in a child known to have an inherited form of rickets. The possibility of alfalcacidol toxicity was excluded on the basis of clinical history, unchanged urinary calcium/creatinine ratios, and stable values for serum calcium. It also seemed unlikely that either lack of compliance or sudden treatment failure was involved. A brief "wait and watch" policy was adopted, with the expectation that a rapid decrease in serum activity of alkaline phosphatase would vindicate the presumptive diagnosis. I encourage others to consider the same approach and to be forewarned of this possibility in children with metabolic bone disease under their care.

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References