CLINICAL AND METABOLIC STUDIES IN HYPOPHOSPHATASIA*

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Hypophosphatasia is a specific, genetically determined metabolic disorder, characterized clinically by abnormalities of bones and teeth, and biochemically by a diminished blood and tissue alkaline phosphatase activity and the urinary excretion of phospho-ethanolamine (PEA). The disease is usually obvious at birth when the manifestations are most severe, but may present at any age thereafter.

Five cases were studied. Four developed in infancy, one in adult life. There were no neonates. The results are noted briefly below. All showed the biochemical defect.

Clinical Aspects

Three children, including a monozygotic twin, presented solely with spontaneous shedding of the anterior deciduous teeth, commencing at 18 months of age. Bone radiology was normal. One child with classical changes on bone X-ray had a clinical picture suggesting rickets, with delayed motor development and bowing of the legs. An X-ray of the distal radius and ulna, taken at the age of 2 years, showed marked cupping and erosion of the metaphysis. In addition there were areas of radio-lucency which corresponded to islands of uncalcified osteoid and cartilage. Spontaneous healing was noted during the course of a year. The adult presented with spontaneous fractures associated with diffuse undermineralization of the skeleton. This latter case was studied for some months in a metabolic ward, during which time a good correlation between the serum alkaline phosphatase levels and PEA excretion was found—in that below 4 - 5 SJR units,[1] PEA was consistently excreted. (Normal values 4 - 8 units.) Quite wide fluctuations in alkaline phosphatase activity occurred, both spontaneously and in response to an acute magnesium infusion, when the levels rose.

Genetics

Four family studies, one extending through 4 generations, showed a typical recessive inheritance—the heterozygous state being characterized by the biochemical abnormality, with no clinical or radiological suggestion of bone or tooth disease.

Pathology

In the adult case, biopsy of the 11th rib was undertaken after ingestion of tetracycline. Undecalcified sections were stained by the method of Frost[2] and examined under normal and ultraviolet light. Excess osteoid was clearly shown. Actively remodelling osteons were reduced to 25% of normal, but these 25% appeared to be forming bone at a normal rate (1 μ/day).

Sudan black staining by the method of Irving,[3] thought to be specific for phospholipid, suggested a marked diminution of the characteristic 'sudanophilia' observed normally during the initial stages of calcification of osteoid.

Electron microscopy showed a diminution in osteoblastic endoplasmic reticulum. Osteoid was qualitatively abnormal, showing an atypical fine network of collagen fibrils, 80 - 90 A wide, without characteristic banding.

Examination of the teeth of childhood cases by routine histologic methods showed the essential defect to be an aplasia of the cementum.

Metabolic Studies

PEA was demonstrated by high voltage electrophoresis[4] followed by chromatography in the second dimension, in a butanol, pyridine and water mixture. The PEA spot stained both with Ninhydrin and Hanes-Isherwood molybdate reagent[5] and was easily identified.

In the adult case a number of investigations were pursued. Calcium balance was negative only on extreme calcium depletion (10 mEq./day). The skeleton showed no abnormal avidity for an infused calcium load (12 mg. Ca/kg.). Parathyroid function is measured by serum calcium and phosphorus, and the percentage tubular reabsorption of phosphate[6] was normal.

Stable strontium kinetics[7] were abnormal. A low turnover rate and lowered rate of bone deposition were found (Table I). This correlated well with the histological observations.

TABLE I. STRONTIUM KINETICS

	Exchangeable pool (*litres*)	*Total turnover rate* (*l/day*)	*Urinary excretion rate* (*l/day*)	*Bone deposition rate* (*l/day*)
Hypophosphatasia	43·4	10·7	4·3	6·3
Normal range	42·7 ± 1·1	13·5 ± 0·6	3·9 ± 0·2	9·6 ± 0·4

EXPERIMENTAL INDUCTION OF HYPOPHOSPHATASIA

Magnesium depletion in young rats markedly reduced the alkaline phosphatase activity, with associated PEA excretion. Magnesium refeeding reversed these changes, providing a possible experimental model of the disorder.

CONCLUSIONS

The presence of abnormal osteoid suggests that this may be as important as the low alkaline phosphatase in the genesis of the markedly lowered bone formation and strontium accretion found in hypophosphatasia. Furthermore, the characteristic excretion of PEA, a phospholipid degradation product, and the reduction in 'sudanophilia', point to the involvement of phospholipids, at least in bone, in this disorder. This implies their possible physiologic significance in the calcification process, since they not only form a vital constituent of osteoid, but might act as a substrate for alkaline phosphatase.

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