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Metabolic Bone Disease in Children

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The first two presentations of this session concerned inborn errors of metabolism that present during infancy or childhood: carbonic anhydrase II deficiency, and hypophosphatasia. Each is a rare but instructive enzymopathy that impairs one "end" of the bone remodeling process.

Osteopetrosis with Renal Tubular Acidosis and Cerebral Calcification: The Carbonic Anhydrase II Deficiency Syndrome

Sly (1) described how the autosomal recessive syndrome of osteopetrosis/renal tubular acidosis/cerebral calcification, first reported in 1972, was found in 1983 to be a new inborn error of metabolism. Selective absence of the carbonic anhydrase II (CA II) isoenzyme was discovered in patient erythrocytes, and half-normal CA II levels were demonstrated in the red cells of obligate carriers. Deficiency of this isoenzyme remains to be shown in bone and kidney tissue. Thirty patients have been reported to date. Clinical expressivity is variable but generally resembles "intermediate" forms of osteopetrosis. Radiographs show a developmental form of generalized osteosclerosis with features typical of osteopetrosis that may improve with aging; cerebral calcification is widespread on computed tomography. Most patients have both a proximal and distal renal tubular acidosis. Histopathologic study of bone reveals evidence of unresorbed primary spongiosa—a characteristic feature of all human forms of osteopetrosis. Sly discussed what this new inborn error of metabolism reveals concerning the physiological role of CA II, including a likely function in osteoclast-mediated bone resorption.

Pediatric Forms of Hypophosphatasia

Hypophosphatasia is an inheritable form of rickets/osteomalacia that is characterized by deficient activity of the tissue nonspecific (liver/bone/kidney) isoenzyme of alkaline phosphatase (TNSALP); placental and intestinal ALP activity is unaffected (2). Clinical expressivity is extremely variable and ranges from intrauterine death from profound skeletal undermineralization to onset of recurrent, slowly healing stress fractures in adult life. Premature loss of deciduous teeth is the most sensitive clinical manifestation in children. Rickets occurs although serum levels of calcium and phosphate are not subnormal. There is no effective medical treatment for hypophosphatasia, but early prenatal diagnosis of severe forms is possible. Three phosphocompounds—phosphoethanolamine, inorganic pyrophosphate (PPi), and pyridoxal-5^1-phosphate (PLP)—accumulate endogenously. The recent discovery that plasma PLP levels are elevated in all patients with hypophosphatasia indicates that TNSALP functions as an ecto-enzyme to regulate extracellular, but not intracellular, levels of a variety of phosphocompounds. Identification in 1988 of a missense mutation in the TNSALP gene in a patient with classic perinatal (lethal) hypophosphatasia provides unequivocal evidence for a role for TNSALP in skeletal mineralization. Absence of ecto-TNSALP activity results in extracellular accumulation of PPi, an inhibitor of hydroxyapatite crystal formation, which could account for the defective skeletal mineralization (2).

Williams Syndrome

Chesney (3) described the Williams syndrome. Affected children characteristically have a variety of phenotypic abnormalities including elfin facies, microcephaly, stellate iris, epicanthal folds, and cardiac defects including supravalvular aortic stenosis. Mental deficiency and characteristic personality traits help to make patients relatively easy to identify. Hypercalcemia occurs in about 15% of subjects and is associated with failure to thrive, calcification of the media of blood vessels, hypercalciuria, and nephrocalcinosis. The Williams syndrome is generally a sporadic disorder, but familial cases have been reported. Chesney reviewed what is known about the pathophysiology of the hypercalcemia, including evidence for enhanced sensitivity to vitamin D with excessive intestinal absorption of calcium and evidence for a possible defect in calcitropic hormone regulation, since clearance of intravenously administered calcium is decreased in the Williams syndrome.

The Molecular Basis of Clinical Heterogeneity in Osteogenesis Imperfecta

Byers et al (4) discussed the molecular basis for the clinical heterogeneity of osteogenesis imperfecta (OI). It is now clear that most clinical forms of OI result from mutations that affect the expression or structure of the genes that form type I collagen. Following a description of type I collagen biosynthesis, Byers et al summarized the specific biochemical and molecular defects which have thus far been shown to cause the various clinical (Sillence) types of OI. In addition to the rare instances of gene deletion or large rearrangements, more commonly a variety of point mutations are now being identified in the different forms. Previously it was believed that severe type II OI was in-

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herited as an autosomal recessive trait, but now it appears from molecular biological studies that this form results more commonly from sporadic mutation or, when siblings are affected, from genetic mosaicism. Accordingly, the occurrence risk is considerably less than the 25% for true autosomal recessive disorders. The authors reviewed the relationship between the clinical phenotype in OI and the nature of the specific molecular defect. Our rapidly improving comprehension of the molecular basis for this clinically heterogenous disorder should help to direct potential medical therapies for the various types of OI.

Neonatal Disorders of Mineral Metabolism

Hillman (5) reviewed the neonatal disorders of mineral metabolism, including early and late neonatal hypocalcemia and mineralization problems in premature and term infants. Controversies regarding the diagnostic criteria for early neonatal hypocalcemia and the need for therapy were discussed. The necessity of using biochemical criteria, based upon serum ionized calcium rather than total calcium determination, was emphasized. The mineral and hormonal changes of early and late neonatal hypocalcemia were reviewed, and the role of hypomagnesemia in the latter condition was emphasized. Hillman discussed how, in term infants, disorders of skeletal mineralization are often related to vitamin D deficiency. However, in premature infants fed breast milk, osteopenia/rickets has resulted from inadequate delivery of mineral to the skeleton. She emphasized the role of both phosphorus and calcium supplementation for correction of this problem and reviewed areas where further research is necessary. Hillman's presentation was followed by an interesting discussion session which emphasized the role of placental function in regulating skeletal mineralization of the fetus.

Vitamin D Resistant Hypophosphatemic Rickets: Pathogenesis and Medical Treatment

Glorieux (6) discussed the clinical expression, pathogenesis, and medical treatment of vitamin D resistant hypophosphatemic rickets (VDRR). Controversy continues as to whether this most common form of inherited rickets in North America results from the elaboration of a humoral factor that causes selective renal phosphate wasting or from a more generalized cellular defect that involves the gut and bone as well as kidney. The mouse model for VDRR continues to provide useful information. In 1987, the gene for VDRR in humans was mapped to the distal part of the short arm of the X chromosome. Characterization of the aberrant gene and its product now becomes feasible. Glorieux described how phosphate supplementation together with administration of calcitriol has resulted in improved growth rate, radiographic healing of rickets, and, in some subjects, correction of the mineralization defect at trabecular bone surfaces. The discussion following Glorieux's presentation concerned how hyperparathyroidism provoked by phosphate supplementation can be minimized in VDRR and what effects this medical regimen has on the kidney of these patients.

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