HYPOPHOSPHATASIA

A METABOLIC DISEASE WITH IMPORTANT DENTAL MANIFESTATIONS

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Hypophosphatasia may be described briefly as a condition mostly occurring in infants and children, in which there are rachitic bone changes with a variable degree of hypercalcaemia, and a lowered serum alkaline phosphatase (normal levels, adults 3.7-13.1 K.A. units/100 ml., children 15-20 K.A. units/100 ml.). Urine analysis by paper chromatography shows the presence of a spot corresponding to phosphoethanolamine, which is excreted in small amounts and is considered pathognomonic.

While the bone lesions in hypophosphatasia have been extensively studied, the dental changes, which are equally striking, have been less so. We present here our conclusions from having observed 10 cases of hypophosphatasia, studied with particular reference to the teeth, of which 4 illustrative cases are briefly described.

Case Reports

Case 1. (A.H.). This boy was first investigated when 2½ years old for bony deformities which had been present since birth. He had also had bouts of vomiting which occurred after meals, lasted two day and recurred at six-weekly intervals, and were accompanied by extreme fatigue. At this time he was able to walk, but with a pronounced roll and tended to drag his toes. Both arms and legs had been short since birth and both femora were bowed, the knees were not fully extended, and he had short trident hands. There was lordosis of the lower spine and sulci on either side of the sternum at the costochondral junction. The face was asymmetrical with left-sided proptosis, and the deciduous incisor teeth were reported lost. The coronal sutures of the skull were heaped up.

Radiographs showed the cortices of the bones to be very thin and several long bones showed evidence of old fractures.

Plasma alkaline phosphatase, 2.8 K.A. units/100 ml. Serum calcium, normal. Paper chromatography of urine showed a large excretion of phosphoethanolamine.

FAMILY HISTORY. Both parents were alive and well, and were not related. The *mother's* alkaline phosphatase

level was low, 2.9 K.A. units/100 ml., and urinary chromatogram revealed a definite slight excess of phosphoethanolamine. The *father's* alkaline phosphatase level was also low, 3.8 K.A. units/100 ml., and his urine contained a small amount of phosphoethanolamine. Both parents were, therefore, considered to be heterozygotes for the defect under discussion.

There was one sib, a brother 6 years older than the patient who now at the age of 8 years was well, though at the age of 2 years he had for six months had intermittent bouts of vomiting. Clinically and radiographically his bones were normal, but his alkaline phosphatase level was low, 8.3 K.A. units/100 ml., and his urine contained considerable amounts of phosphoethanolamine.

At 7 years the patient was referred for dental opinion with this typical history of infantile hypophosphatasia. He was now a small child for his age, with some frontal bossing. He was unable to run much, suffering pains in feet and legs. The alkaline phosphatase level, which had fallen to 0.7 units at the age of 5½ years, had risen but was still at a low level, 2 K.A. units/100 ml.

On examination the following teeth were present:

6	E	D	S	D	E	6
6	E	D	I	I	E	6

The first permanent molars were hypocalcified and carious and the second deciduous molars were also hypoplastic and showed extensive attrition. The midline supernumerary was conical, loose, and tilted labially.

Radiographic examination showed the presence of a second midline supernumerary, and all the permanent teeth were present, but the enamel was very thin in both primary and secondary dentitions and showed gross hypoplasia. The alveolar bone appeared atrophic. The following teeth were removed under general anaesthesia:

6	5	5	6
6	D		6

At 8 years the following teeth were present:

E	D	I	E
E	21	12	E

All these deciduous teeth and the permanent upper left central incisor were a little loose. The permanent incisors were hypoplastic and radiographically the upper right incisors appeared near to eruption. At 9 years

FIG. 1.—Case 1 at 9 years: intraoral radiographs show $\frac{1}{1}$ is not covered by bone but is unerupted. All the teeth have hypoplastic enamel especially the developing premolars. The erupted teeth have large pulps and thin roots.

(Fig. 1) the following teeth were present, all of which were a little loose: $\frac{E}{E} \frac{6}{21} \frac{D}{12} \frac{1}{E}$, and the phosphatase level

had risen to 3.2 K.A. units. Radiographically there had been practically no growth of the dental tissues in the past year.

At 9½ years this child's height was 45½ inches (115 cm.) and weight 49½ lb. (22.4 kg.). He was attending a normal school and played football. The following teeth

were present: $\frac{E}{E} \frac{D}{21} \frac{2}{12} \frac{1}{E} \frac{4}{5}$.

The deciduous teeth were very loose and the incisors were grossly hypoplastic but fairly firm.

The patient has been provided with partial dentures overlaying the deciduous molars, providing a larger occlusal table and preventing overclosure of the bite with further loosening of the incisors by occlusal trauma (Fig. 2).

Case 2. (C.N.) This girl presented at 3 months with bowed legs and varus feet which required splinting.

Radiographs showed no evidence of bone disease in the skull or ribs, but some of the lower thoracic and lumbar vertebrae were rather beak-shaped. There was periostitis and metaphysitis of the long bones with bowing, especially of the femora.

At 18 months it was noted that her teeth were falling out and that she had already lost $\frac{A}{A}$, and $\frac{B}{B}$ were very loose, $\frac{B}{B}$ were erupting, and there appeared to be some recession of the gums. There was considerable alveolar resorption in the upper incisor region radiographically, but the bone structure of the long bones had improved and there appeared to be less bowing. A provisional diagnosis of rickets was made.

The serum alkaline phosphatase was 5.3 K.A. units; serum calcium and phosphorus normal.

Before the age of 2 years all the primary incisors had been lost except the lower laterals which were loose as were the upper canines.

By 4 years all the incisors and canines had been lost and the deciduous upper right first molar was loose. There was, however, no evidence of the permanent dentition. Radiographically the bone was approaching normal compared with the coarse trabecular pattern suggestive of an earlier generalized decalcification which had been present a year before.

At 5 years, though small, height 36½ in. (91.5 cm.), weight 24½ lb. (11.2 kg.), the child was fit and well but

FIG. 2.—Case 1 at 10 years: there is severe pitted hypoplasia of the enamel especially in the upper teeth.

FIG. 3.—Case 2 at 9½ years: the rate of tooth development is normal but the enamel and the roots of the incisor teeth are thin and there is spacing of these teeth.

still had a deformity of the right foot. The alkaline phosphatase level had risen to 10 K.A. units/100 ml. Urine chromatography confirmed the diagnosis of hypophosphatasia, by showing a phosphoethanolamine spot.

Radiographically there were deep indentations in the iliac crests with areas of defective ossification in the outer aspects of the femoral necks. There was no abnormality of the skull other than brachycephaly, and the sutures were patent. Only the deciduous second molars were present, and these showed extensive cervical resorption.

At 6 years the lower first permanent molars were erupted, they were firm but hypoplastic. The serum alkaline phosphatase had now risen to 15 K.A. units.

At 6½ years the lower central incisors were not present and both the upper deciduous second molars were loose. At 8 years all the incisors were erupted, except the upper laterals, and there was a large diastema between the upper centrals. The following teeth were present but loose and carious:

E				
E	D		D	E

No further tooth eruption took place in the following year but the diastema was slowly closing.

At 9 years and 5 months, when the serum alkaline phosphatase level was 6 K.A. units/100 ml., dental development was normal, the following teeth being present:

6	4	2	1	1	2	4	6
6	3	2	1	1	2	3	6

The first molars had early caries and the lowers had early lingual decalcifications. 1 1 were proclined with an increased overbite and central diastema, 1 1 were slightly retroclined. The tooth/bone ratio was high (Fig. 3).

The patient continued fit and well, but at 11 years and 4 months it was noticed that the upper incisors were loose, and required splinting with a bite plane plate and labial bow wire. During the following 9 months these teeth became firmer but there were intermittent periods of loosening. Radiographically these teeth were vital but there was little alveolar bone; 1 which clinically was the loosest tooth appeared a little extruded from the socket and apically slightly resorbed. This tooth was dislodged and lost by a light blow on the mouth.

At 13 years the patient still wore the splint, and 6 6 were both carious. Radiographically 6 6 showed gross resorption, the second premolars were submerged and there was marked thinning of the lamina dura in both upper and lower incisor and canine regions with recession of the alveolar bone. Enamel on the incisors and the

roots of all the teeth appeared thin. The four first molars were extracted at which time it was noted that the mesial root of 6 and the mesiobuccal root of 6 had been completely resorbed away and the pulp chambers exposed. There was considerable resorption on the mesial aspect of 6 with near exposure of the pulp. The roots of these teeth were both short and rather thin. The tips of all the cusps were hypoplastic, and all these teeth had occlusal fillings (Fig. 4).

At 13 years the patient continues well with a normal growth rate, though she is very small for her age. The following teeth are present:

7	4	3	2	1	1	2	3	4	7
7	4	3	2	1	1	2	3	4	7

but the upper incisors are a little loose and the splint is still worn.

Case 3. (S.L.) At birth it was noted that the girl had short arms and legs with bowing of the long bones, and dimples of each limb, but was otherwise normal. Later she refused feeds and had occasional bouts of vomiting; there was a tendency to constipation and she failed to thrive. Cranio-facial development was small but of normal ratio, the thoracic cage was small with palpable enlargements of the costochondral junctions.

The serum alkaline phosphatase was 7.6 K.A. units/100 ml., and the urine chromatograph had a hypophosphatasia pattern. Radiographically, a generalized upset in bone formation at the growing ends of the long bones with sites of multiple healed old fractures was seen.

At 2 years, marked bulging of the anterior fontanelle with premature synostosis was present. All the deciduous incisor teeth had been lost, with no evidence of radicular resorption.

At 3 years bilateral papilloedema necessitated bilateral coronal craniectomy. The serum alkaline phosphatase at this time was 5.9 K.A. units.

Case 4. (M.M.) At 15 months it was noticed that this little girl had a peculiarly shaped skull, and by 2 years had genu valgum. The serum alkaline phosphatase level was 2.4 K.A. units/100 ml.

All the deciduous incisors had been lost by the age of 4 years (Fig. 5).

A year later papilloedema resulting from craniostenosis necessitated bilateral coronal cranioplasties. That condition, however, continued to worsen, and going into renal failure she died before her sixth birthday.

FIG. 4.—Case 2 at 13 years: there is extensive alveolar resorption especially in the incisor region and the roots of the lower incisors are very thin, the $\underline{I}$ is elevated in the socket, the second premolars are impacted, and there is considerable resorption of the roots of the first permanent molars.

Dental Radiographic Findings

Most cases exhibit early resorption and loss of the deciduous teeth especially the deciduous incisors, but there is no compensatory early eruption of the permanent teeth, nor is there any constant delay in eruption. Not infrequently deciduous teeth are exfoliated with very little evidence of resorption. The pulp cavities in the deciduous teeth appear

considerably larger than normal and those in the permanent teeth also seem slightly larger.

Thickness and density of the lamina dura and the width of the periodontal space appear to be normal in most cases, but the layer of cementum on the permanent teeth is thin.

Hypoplasia of the deciduous teeth, the permanent incisors, and first molars is a constant finding and

FIG. 5.—Case 4 at 5 years: early loss of the anterior deciduous teeth, large dental pulps, thin roots in the erupted teeth, and hypoplasia of the developing teeth.

some cases show hypoplasia of other permanent teeth also.

Dental Histology

Three typical examples are described.

1. (Case S.H.). A slightly carious deciduous lower second molar, which had been exfoliated early, was decalcified, stained with haematoxylin and eosin, and sectioned mesiodistally.

The dentine appeared normal and the pulp chamber was largely occluded by secondary dentine, the remaining space being occupied by strands of degenerative pulp tissue. A small amount of resorption had taken place at the apex of the roots and there was evidence of earlier resorption. Cellular secondary cementum was confined to the apical third of the root.

A ground section of the deciduous upper lateral incisor which was also exfoliated early, with little evidence of resorption, showed that the enamel and dentine were normal though the incremental lines in the dentine were accentuated. The cellular cementum was confined to the radicular apex and there were only a few Howship's lacunae present, showing that there had been practically no resorption.

2. (Case S.L.). A lower lateral incisor which had been shed early: there was no apparent resorption of the root and the apex was wide open and the enamel appeared normal. A mesiodistal decalcified section showed that

the dentine had a typical scalloped edge corresponding to the amelodentinal junction, the tubules appeared swollen coronally and stained densely. There was considerable occlusion of the pulp by normal secondary dentine. The cementum was practically non-existent and there was no evidence of resorption.

3. (Case S.H.). Microradiographic section of a deciduous canine which was normally shed, but again lost early, on examination showed evidence of only a small amount of resorption. The enamel was slightly hypoplastic and most had been shattered and lost in sectioning. There was a well-defined granular layer of Tomes in the radicular dentine just below the crown, and the coronal pulp had been occluded by secondary dentine. The radicular pulp chamber was still wide with a bar of calcified tissue across the apex where some resorption had taken place. The layer of cementum was thin, with patches of resorption where the cementum has been completely lost together with a small amount of dentine. There were scattered patches of calcified tissue in the root canal and a shadow corresponding to the predentine.

Function of Alkaline Phosphatase in Development and Formation of Teeth

In the developing tooth germ alkaline phosphatase first appears in the differentiating stellate reticulum: this was considered by De Fazio (1954) to be associated with mineralization. Symons (1954) suggested that mineralization occurred later in development and that the enzyme reflected active cellular differentiation. This was not supported by earlier work of Morse and Greep (1947) who found little or no phosphatase activity in various sites of proliferation in the rodent tooth germ or in the epiphyseal plate of growing bones.

The presence of alkaline phosphatase in the stellate reticulum is believed to be important for the liberation of the carbohydrate radicle from hexose-phosphate and its synthesis to mucopolysaccharides (Moog and Wenger, 1952; Kroon, 1952). According to Butler (1956) and Ten Cate (1957) acid mucopolysaccharide produced by the reticulum cells of the stellate reticulum assists in the determining of crown pattern. Phosphatase activity also occurs in the external enamel epithelium and is presumed to be associated with the transfer of phosphorylated glucose across the cellular barrier. Alkaline phosphatase is most active in all parts of the enamel organ when the matrix is being laid down, that is when the ameloblasts are most active and nutrient transfer greatest (Johnson and Bevelander, 1954). However, there is no evidence of phosphatase activity within the ameloblasts in the human tooth germ up to and including enamel matrix formation (Ten Cate, 1962; Chèvremont and Firket, 1953).

Similarly the absence of cytoplasmic alkaline

phosphatase activity has been reported during dentinogenesis in human odontoblasts (Ten Cate, 1962). Since both ameloblasts and odontoblasts produce a calcified tissue and are devoid of alkaline phosphatase and since both are related to a cell layer rich in phosphatase in the stratum intermedium and the subodontoblastic zone respectively, it is reasonable to suppose that both these enzyme-rich structures are associated with the production of a calcified tissue.

Three possible functions of alkaline phosphatase in relation to calcified tissues have been postulated by Bourne (1956): it may (a) assist in the formation of an organic matrix, (b) provide a phosphate ester template for the crystallization of bone salt, or (c) keep the surface of bone crystals free of ester phosphatase for the continued growth of crystals. The two latter postulates are not supported by the work of Lefkowitz, Bodecker, and Shapiro (1944) and Barnum and Armstrong (1941).

Phosphatase is associated with the production of mucopolysaccharide which is linked to both fibrillogenesis (Gersh and Catchpole, 1949; Curran, 1953; Buck, 1953) and the formation of collagen (Bourne, 1943; Buck, 1953).

It is not known whether the enzyme plays a direct or indirect role in the formation of collagen, but sulphated mucopolysaccharide, the ground substance of the dentine, is elaborated by the pulp (Bevelander and Johnson, 1955), and the intense enzyme activity in the subodontoblastic area may be associated directly with this, or indirectly with fibrillogenesis.

A fibrillar ground structure at the beginning of enamel matrix formation has been demonstrated (Nylen and Scott, 1958; Scott and Nylen, 1960).

Fearnhead (1960) demonstrated a granular precursor in the ameloblasts, which was passed through the cell wall in the terminal bar region and became orientated as definite fibres.

The function of alkaline phosphatase in the stratum intermedium is believed to be associated with the elaboration of mucopolysaccharide which passes between the ameloblasts and forms a template for the aggregation of the protofibrils (Meyer, 1947, 1950).

It is now believed that alkaline phosphatase plays no direct part in the precipitation of mineral salts.

Treatment

At the present time there is no satisfactory medical treatment for this disease. Vitamin D has been tried in varying doses, but some authorities have claimed that on occasions this has aggravated the condition. A low calcium diet, however, is generally favoured. If the child survives, the general clinical condition slowly improves but may deteriorate later in middle age (Bethune and Dent, 1960).

Hypoplastic teeth should be protected by strict oral hygiene and attention to dietary habits and the use of fluoride compounds. Prophylactic odontotomy and shell crown coverage should be considered where applicable. Dentures should be provided to prevent overloading the teeth when few are standing, and to splint and support those that are loose.

In view of the high tooth/bone ratio, it may be advisable, in treating the overcrowding, to remove the first permanent molars, which are usually hypoplastic and prone to caries.

Conclusions

Hypophosphatasia of severe intensity, occurring during the time when dental tissues are being formed, results in hypoplastic deficiency and reduction in the thickness of enamel. Many deciduous teeth are lost very early, especially the incisors, and they are often lost with very little resorption of the roots. There is no compensatory early eruption of the permanent teeth and the incisors and first molars are often hypoplastic.

The permanent incisors, especially the uppers, become loose early and suffer periods of looseness and relative firmness. The cementum layer is rather thin and the loosening of these teeth is probably associated with the breakdown of the periodontal attachment under normal function. Splinting the teeth after loosening has occurred has no real long-term effect. These observations tend to reinforce the view that alkaline phosphatase is, among other functions, associated with the production of the organic matrix for enamel formation and with the production of collagen.

The jaws of these patients tend to be small, so that a high tooth/bone ratio results. Early loss of the hypoplastic first permanent molars due to caries often results in collapse of the bite.

Summary

Ten cases of hypophosphatasia have been studied with particular reference to the dental lesions.

Dental lesions are prominent in this disease, and consist of hypoplastic deformity, with crowding and early loss of the teeth in both dentitions.

The role of phosphatase in the development of the teeth is discussed.

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