Hypophosphatasia *

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In a previous lecture I discussed a metabolic disorder, idiopathic hypercalcaemia, that has recently been recognised in England and elsewhere, in which the raised serum calcium probably results from an individual hypersensitivity to Vitamin D. Renal damage, skeletal changes and, in some instances, mental impairment are the main results.

I would now like to bring to your notice another condition, hypophosphatasia, in which hypercalcaemia is also a prominent feature and likely to cause the same trouble in the kidneys, but mental development is not affected. Although the bone disorder is very different in these two diseases, tending to be osteosclerotic in one and osteoporotic in the other, craniostenosis is a possible complication of both.

Recent research has demonstrated that errors of metabolism are associated with diverse children's diseases, the cause of which has hitherto remained obscure. Several examples can be quoted, such as phenylketonuria, galactosaemia, progressive lenticular degeneration (Wilson's disease) and goitrous cretinism. In all these there is a block in metabolism, so that the final essential amino acid or enzyme is not available. Heredity plays a significant part in most of these disorders, which either figure in the family history or are found in some of the siblings. Sometimes this is only represented by a 'trait' in the parents or other members of the family, who are otherwise quite healthy. This trait is recognised by discovering an identical abnormal amino acid pattern in the urine to that found in those suffering from the actual disease.

In hypophosphatasia the deficient enzyme is alkaline phosphatase and the intermediate metabolite in the urine, phosphoryl-ethanolamine.

Rathbun[6] originally suggested the term 'hypophosphatasia'. We became interested in the condition seven years later.[7], when we had under our care an infant with hypercalcaemia, renal insuffi-

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ciency and widespread radiological changes in her bones rather like rickets. At the time the diagnosis proved very puzzling, but since then we have seen seven other cases, which we have been able to follow for some years. Recently Fraser [3] has reviewed the subject extensively and has collected 35 examples of the disease from various parts of the world.

Clinical Picture

There is no doubt that the disorder can already be present during intrauterine life. It has in fact been diagnosed radiologically before birth, when a previous sibling had died of the disease and it seemed probable that the next child might also be affected [5].

Sekeletal Changes. In others extensive skeletal lesions become obvious during the first few weeks of life, and in three this caused extreme shortness of the limbs, which was immediately noticed by the parents. On examination marked costo-chondral beading and prominence of the ends of the long bones can be made out, similar to those seen in severe rickets. But it is the skull which attracts the most attention. The cranial vault is usually represented by four plaques of thin bone, separated by wide sutures and large fontanelles. This poorly ossified vault is obviously a weak presenting part during labour, and although this proceeds normally, it may not be without trauma, and two of our infants suffered from a subdural haematoma as a result, one of which later required surgery. Before long, still in infancy the picture changes. Continual failure of normal ossification at the suture lines prevents proper increase of skull circumference and cranial capacity to accommodate the rapidly growing brain. Under increased intracranial pressure the anterior fontanelle bulges and finally closes with a heaped up prominence, through premature and disorderly calcification. At the same time the widely separated sutures are speedily filled in by calcifying tissue deposited in their gaps, producing *craniostenosis* at an early stage and possibly visual disturbances.

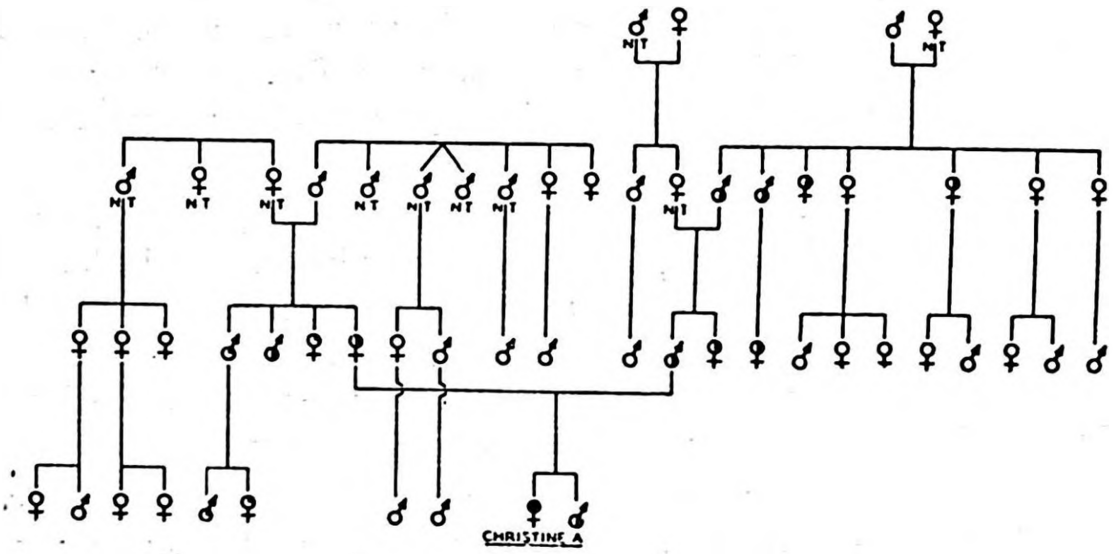
As children with this disease grow older, they are often seen to have a certain degree of proptosis, a globular head and a silver beaten X-ray appearance of the skull. By that time the sternum is flattened, the anterior-posterior dimension of the thorax is decreased and the normal curves of the vertebral column are absent.

Symptoms and Blood Chemistry. The earliest symptoms are those we have already met in hypercalcaemia — vomiting, constipation, anorexia and failure to thrive. Raised serum calcium levels are invariably found in severe cases with lesions dating from birth or soon afterwards, and in a proportion when these develop later. Hypercalcaemia

was discovered at some stage in 5 of our 8 children and might well have been present in all, had the tests always been made at the outset. Raised intracranial pressure is probably an additional cause of the vomiting, and with the marked anorexia physical development is severely retarded. Intelligence on the other hand is never affected. As in other conditions with hypercalcaemia, renal function may become impaired, blood urea levels are correspondingly raised at the time, and there may be hypertension. In the severest cases serum cholesterol figures are also above normal. Fortunately in most instances these biochemical changes are temporary and in course of time revert to normal. The kidney damage is reversable and causes no further trouble, but this is not always so and one of our children ultimately died of renal failure with gross hypertensive changes.

In general the serum inorganic phosphorus levels are normal. As already indicated, the cardinal defect in this condition is in alkaline phosphatase production. This can be demonstrated in all tissues where this enzyme is normally present; but the deficiency is most evident in the skeleton, where its presence in adequate amounts is required for normal ossification. The blood level is consistently low, particularly when this is related to the bone defects, which should under other circumstances provoke an increased production of this enzyme. Great variations will however be found in the blood level on repeated examination. This is understandable, since the amount found in the blood is only a very rough estimate of what is being produced in the rest of the body. Nevertheless it is surprising to find that the blood phosphatase level remains low even when ossification eventually begins to progress in a normal fashion. This can hardly be explained on the basis that the rate of bone growth has reached a relatively slower stage, since recovery often begins when the child is still very young.

Radiology. The main defect appears to be patchy calcification at the metaphyses and growing edges of the bones, producing an irregular and ill defined margin. This varies in degree; in some the whole skeleton is involved, in others certain regions which are not growing points escape, as for example the upper end of the femur. The metaphyses are more severely involved than the epiphyses, but here as well calcification is abnormal. Bowing may be present and 'greenstick' fractures are sometimes visible; the rib ends are expanded, demineralized and ill defined. The periosteum is elevated, due to early irregular formation of new bone. This and the absence of cupping at the growing ends of the bones give the X-ray picture a different appearance from that of rickets.



Family tree of C. A. (see Table), showing members of the family with abnormal amounts of phosphorylethanolamine in the urine on chromatography.

○ $^1/_2$ black = large amounts of this amino acid.

○ $^1/_4$ black = small but significant amounts.

C. A. was a clinical case of hypophosphatasia and her brother showed a "trait„ of this disorder.

Osteoporosis is particularly well marked in the skull at an early stage; later, as already mentioned, amorphous calcification causes premature fusion of the sutures and craniostenosis.

The *teeth* of first dentition develop normally, but they nearly always fall out prematurely, probably due to poor alveolar ossification and an abnormal lamina dura. Permanent dentition proceeds in a regular way, but severe caries is likely to supervene.

Histology of the bones demonstrates extensive areas of cartilage and osteoid with grossly abnormal calcification. Osteoblasts and osteoclasts are generally scanty at the margins of the trabeculae, and osteocytes are only moderately well represented.

Heredity. We have already indicated that the discovery of increased amounts of phosphorylethanolamine in the urine can be taken as a hallmark of the disease. With this in view the families of our cases have been investigated[1], and it would seem that the disorder is determined by an autosomal recessive gene. Clinical evidence of the disease is only likely to become manifest in a child of two parents who are carrying the gene as heterozygotes. The family tree of one such case is presented (see Figure).

Prognosis. All our cases except one ultimately recovered, the bone defects disappeared and ossification proceeded in a more normal manner. The bowing observed early in life straightened to a remarkable degree, but limbs which were noticed to be short at

birth have not since grown to a normal length, and all the children remain rather stunted. No relapses take place once recovery has occurred, though adults who have suffered from the disease in childhood are apt to have brittle bones, and minor fractures are sometimes visible radiologically [1].

Quite a number of deaths have been recorded, and the prognosis is particularly bad when the disease begins in foetal life, if the phosphatase deficiency is extreme, or the hypercalcaemia has been severe enough to damage the kidneys irrevocably. This occurred in one of our series, a girl of six years, with symptoms from the age of eight months, who died of renal failure after a long illness.

One other complication must be mentioned, which is a direct result of the craniostenosis. Three of our children developed papilloedema and we were only able to save the sight by surgical reconstruction of the sutures. In one other infant, who had very marked raised intracranial pressure, the procedure was undertaken as a prophylactic measure. It is certainly wise not to wait too long before deciding upon surgery, since firm attachment of the dura to the inner surface of the calvarium may occur later, and the dura can be badly torn during the operation, leaving a permanent leak of cerebro-spinal fluid under the scalp (see Table).

Cause. The exact pathogenesis of the disease is not clear. We know that alkaline phosphatase is deficient, and most people now believe that the principal role of this enzyme is concerned with an adequate preparation of organic bone matrix in which phosphorus and calcium salts can be laid down. There is no evidence of excessive loss of phosphatase in the urine, faeces or saliva, and it seems more likely that the osteoblasts, normally the principal source of this enzyme, are not functioning properly in this respect. The paucity of these cells on histological examination of the bones, which has been demonstrated in some cases at the height of the disease, is therefore of some significance. No inhibitor of cellular function has so far been discovered.

Certain investigators have suggested that Vitamin D hypersensitivity is a factor, with a low alkaline phosphatase as a secondary effect, but studies have indicated no more than a normal positive calcium balance. General decalcification of bone is never seen, except in the terminal stages of renal failure, and then the parathyroids are found to be normal.

The cause of the hypercalcaemia is also uncertain, and one must conclude that for some unexplained reason intestinal absorption of

TABLE: 1

Case	Apparent Age of Onset	Early Symptoms and Signs	Teeth	Blood Chemistry (mgm. per 100 ml) Ca.	P.	Phtase	Urea	Cholesterol	Complications	Age last examined	Progress
C. N.	Birth	Short limbs. Failure to thrive.	Premature Exfoliation	10.7	4.6	5.3	13	—	—	7 yrs	Recovery
C. M.	1 week	Vomiting, anorexia, constipation.	ditto	11.6	5.8	2.3	87	191	Craniostenosis, craniectomy	3 yrs	ditto
S. L.	Birth	Short limbs, vomiting, constipation, failure to thrive.	—	14	6.8	7.6	68	95	—	8 mths	Improved ossification
A. H.	Birth	Short limbs, vomiting, failure to thrive.	Premature Exfoliation	10.4	6.4	2.8	45	151	Partial craniectomy	3 $^{3}/_{12}$ yrs	Recovery
E. M.	2 weeks	Vomiting, constipation, failure to thrive.	ditto	12.2	5.9	7	52	228	Craniostenosis, craniectomy	2 $^{4}/_{12}$ ..	Recovering
C. A.	3 weeks	Vomiting, anorexia, failure to thrive.	—	14.4	3.8	3	70	224	Partial craniostenosis	4 $^{8}/_{12}$ ..	Recovered
S. G.	3 months	Vomiting, constipation, anorexia.	—	10.8	4.8	7.3	75	285	Craniostenosis, craniectomy.	4 $^{9}/_{12}$ ..	Recovered
M. M.	8 months	Genu valgum, failure to thrive.	Premature Exfoliation	12.6 6.8	3.5 5.3	3	296	368	Renal failure.	5 $^{1}/_{2}$ ..	Death.

Table showing main features and biochemical changes. Highest calcium and lowest alkaline phosphatase figures are recorded from a series of tests. The blood urea level is given at the height of the disease. Except for M. M., the biochemical changes reverted to normal, though the phosphatase remained at a low level. The final low calcium figure in M. M. was due to renal failure.

calcium is in excess of the patients' ability to deposit the material in his bones.

Finally it seems odd that with failure of mineralisation at the growing points of the rest of the skeleton the bones of the skull should proceed otherwise and unite prematurely. Since normal growth ceases at their margins, they presumably fuse as a result of amorphous calcification.

Obviously many problems in this disease are still obscure and further research is required before they can be settled.

Treatment.

Several investigators have tried the effect of giving Vitamin D in high dosage and have reported a beneficial effect. But in face of hypercalcaemia this would appear to be illogical and a risky measure, only likely further to increase renal damage. Our principle in treatment now is to reduce the calcium intake and the amount of Vitamin D, so as to lower the blood calcium and take the strain off the kidneys. In this way spontaneous recovery, which is the trend in the majority of cases, can proceed with less danger of renal complications. Cortisone has been recommended as a remedy[2] but we have been unable to confirm any beneficial effect. Surgical relief of craniostenosis to save sight has already been mentioned.

Summary.

Here then is another disorder in which hypercalcaemia is the most prominent biochemical result. It carries with it the risk of renal damage, which may at times prove fatal. The disease must be differrentiated from rickets, congenital syphilis and hyperparathyroidism, but there is plenty of clinical and pathological evidence to exclude all these. It is an example of an hereditary disorder, confirmed by discovering grossly abnormal amounts of phosphorylethanolamine in the urine on chromatography. Beyond finding a persistently low alkaline phosphatase in the blood and many of the tissues, the pathogenesis is unknown and there is no known specific treatment.

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