

## CME Article

# Clinics in diagnostic imaging (I I 2)

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**Fig. 1** Frontal radiograph of the trunk and limbs of the neonate.

## CASE PRESENTATION

A two-hour-old female infant was referred from a private hospital with respiratory distress and short limbs. The patient was born at full-term to a G<sub>1</sub>P<sub>0</sub> 25-year-old mother by caesarean section due to cephalopelvic disproportion. On physical examination, her weight was 2,990 g (25th percentile) with a length of 49 cm (50th percentile) and head circumference of 35 cm (75th percentile). She had normal facial appearance with soft calvarium. Her

forearms and lower legs were short, without anterior bowing or spur projection. Laboratory investigations revealed normal electrolyte and serum calcium at 8.9 mg/dL (normal range for age 7.6-10.4 mg/dL) but serum phosphorous was elevated at 9.6 mg/dL (normal range for age 4.5-9 mg/dL). Notably, the serum alkaline phosphatase (ALP) was very low at 2 U/L (normal range for age 150-420 U/L). What does the neonatal radiograph show (Fig. 1)? What is the diagnosis?

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### IMAGE INTERPRETATION

The neonatal radiograph (Fig. 1) showed short proximal and distal limbs, indicating micromelic dwarfism. There was diffusely-poor ossification, especially at the ribs, long bones of both forearms and both fibulae. The spine showed platyspondyly. The absence of epiphyseal ossification centre at the distal femora and proximal tibiae, which should be seen in full-term infant, was noted. All long bones showed metaphyseal irregularities and cupping, similar to rickets.

### DIAGNOSIS

Perinatal lethal hypophosphatasia (PLH).

### CLINICAL COURSE

The patient received supportive treatment by endotracheal intubation, and was placed on a respirator because of hypotonia and respiratory distress. The arterial blood gas showed moderate hypoxaemia, with acute respiratory acidosis and metabolic acidosis. The respiratory and metabolic conditions were corrected by hyperventilation and sodium bicarbonate infusion. After the neonatal radiograph showed generalised demineralisation and laboratory investigations revealed a very low level of ALP of 2 U/L, the diagnosis of PLH was made. The clinical course and prognosis were explained to the parents. They then wished to take the baby home, and she was discharged from hospital at the age of four days.

### DISCUSSION

Hypophosphatasia is an uncommon inherited disorder (1/100,000 in severe form)<sup>(1-3)</sup> which is manifested by skeletal demineralisation, decrease in activity of bone/liver/kidney serum alkaline phosphatase isoenzyme, tissue-nonspecific alkaline phosphatase (TNSALP) and increased phosphoethanolamine (PEA) in urine. It was first characterised in 1948 by John Campbell Rathbun (1915-1972) who reported the case of an infant who died from rickets, seizure and had low serum ALP activity<sup>(4,5)</sup>.

In humans, there are four ALP isoenzymes encoded by four distinct gene loci. Three are expressed and accordingly named in specific tissue as intestinal, placenta and germ cell ALP. The fourth ALP isoenzyme is plentiful in the liver, bone and kidney and is called TNSALP<sup>(5)</sup>. The disease results from a missense mutation of the TNSALP gene which is located near tip of the short arm of chromosome one (1p36-34)<sup>(3-5)</sup>. Hypophosphatasia has subnormal serum TNSALP activity while the three specific ALP isoenzymes are not decreased. The three main substrates for TNSALP are inorganic pyrophosphate

(PPi), PEA and pyridoxal-5'-phosphate (PLP). If TNSALP function is diminished, the endogenous content of these three phosphocompounds will accumulate. High levels of PPi in urine and plasma will bind to amorphous calcium phosphate and the transformation to hydroxyapatite crystals will be inhibited, explaining the defective skeletal mineralisation and calcium deposition disorder in hypophosphatasia<sup>(2,5,6)</sup>.

Hypophosphatasia is classified into six forms, namely: perinatal (lethal), infantile, childhood, adult, odontohypophosphatasia and pseudohypophosphatasia<sup>(2,5)</sup>. The earlier the skeletal symptoms manifest, the more severe the disorder and the worse the prognosis. The severe forms (perinatal and infantile) are transmitted autosomal recessively, while mild forms can be transmitted in both autosomal recessive and autosomal dominant forms<sup>(3,5)</sup>.

The perinatal (lethal) form is expressed in-utero, causing stillbirth or death within a few days of life, and has the poorest prognosis<sup>(5,7)</sup>. There is a wide spectrum of clinical and radiographical abnormalities in this form. The patient shows short-limbed dwarfism (micromelic type) and bowing of lower extremities (Fig. 2). The calvarium is soft due to profound hypomineralisation, resulting in the "caput membranaceum"<sup>(2,5)</sup> or an appearance like a bag of fluid<sup>(1)</sup>. Skin-covered osteochondral spurs (called Bowdler spurs) may be seen protruding from the midshaft of forearms or legs<sup>(3,5,8)</sup>. They usually underlie dimples on the skin and present at birth, persisting until childhood or even adulthood<sup>(9)</sup>. These spurs only rarely first present in adolescence. If the spurs are seen in an adolescent patient, it is believed that they may indicate the benign perinatal form<sup>(10)</sup>.



**Fig. 2** Clinical photograph of a patient with PLH shows short proximal and distal limbs, indicating micromelic dwarfism.

Polyhydramnios and blue sclera may be seen, resulting in the initial diagnosis of osteogenesis imperfecta type II<sup>(8)</sup>. These patients have respiratory distress from lung hypoplasia and rachitic deformities of the chest. Other symptoms include high pitched cry, periodic apnoea, cyanosis, bradycardia, myelophthisic anaemia and idiopathic seizure<sup>(3,5)</sup>. There is another rare perinatal benign form which exhibits spontaneous improvement of skeletal defects<sup>(3)</sup>.

Radiographs show marked variety from patient to patient. The most notable finding is an extremely generalised reduced or complete lack of ossification. The skull shows a demineralised globular cranium; if there is calcification, it appears first in the occipital and frontal areas<sup>(8)</sup> (Fig. 3). The teeth are also very poorly-formed. In the spine, vertebral bodies are frequently unossified but some show rectangular/round, flattened, sagittally clefted or are butterfly-shaped<sup>(4,8)</sup> (Fig. 4). The posterior elements may be more unossified than the vertebral bodies. The metaphyses show irregularities and flaring or “metaphyseal cupping” like rickets, but in hypophosphatasia, there is prominent radiolucency (“tongue-like”) of unossified osteoids protruding into the central portion of metaphysis<sup>(5,7)</sup> (Fig. 5). This characteristic finding is only present in infancy and childhood. Irregular tongue-like projections may be seen in epiphyses, round carpal bones and talus<sup>(9)</sup>. The shape of long bones can be “chromosome-like” or “campomelic-like<sup>(8,10)</sup>”.

Other radiographical features are poorly-ossified or complete lack of ossification of the ribs (Fig. 6). The clavicles are the least affected<sup>(4,8)</sup> (Fig. 6), and absence of clavicles has not been reported<sup>(6)</sup>. The ossification of the clavicles may help to differentiate hypophosphatasia from severe form of cleidocranial dysplasia (CCD) in which secondary hypophosphatasia results in severe osteopenia and radiographical mimicry of hypophosphatasia. The hallmarks of CCD are hypoplasia/absence clavicles, delayed suture closure and hypoplasia of pubic bones<sup>(6,11)</sup>.

In the infantile form, the clinical signs appear before six months of age, and include features such as poor feeding, premature craniosynostosis and manifestations of rickets e.g. broad wide ankles and wrists, bowing legs and rachitic rosary. The radiographical features are similar to those of rickets, namely: cupping and fraying of metaphyses of long bones with widened growth plates and spotty demineralisation of the epiphyses<sup>(4,7)</sup>. Deformities of the anterior ends of the ribs in hypophosphatasia are widening and irregular cupping, in contrast to the



**Fig. 3** PLH. Lateral skull radiograph shows diffuse demineralisation with calcification in frontal and occipital bone (arrowheads).



**Fig. 4** PLH. Lateral spine radiograph shows flat-shaped (platyspondyly) vertebral bodies with ossified vertebral bodies and posterior elements.



**Fig. 5** PLH. Right leg radiograph shows absent ossification centre of the epiphyses at the distal femur, proximal tibia, talus and calcaneus which should be seen in the full-term infant. The right fibula is poorly ossified. The metaphyses of the femur and tibia show irregularity and cupping. There are prominent radiolucent or "tongue-like" lesions of unossified osteoid protruding into the central portion of the proximal and distal metaphyses of the right femur (arrowheads).



**Fig. 7** Rickets due to distal renal tubular acidosis in a nine-year-old girl. Radiograph of both forearms shows metaphyseal irregularities and flaring similar to hypophosphatasia. The physes are widened from loss of zone of provisional calcification. Delayed bone age is also evident. (Courtesy of Thaworn Dendumrongsup, MD, Songkhla, Thailand)



**Fig. 6** PLH. Chest radiograph shows some of the ribs are poorly-ossified and complete lack of ossification of other ribs, especially in the left side. Both clavicles are well-ossified (arrowheads).



**Fig. 8** Oncogenic osteomalacia from a benign tumour at the left knee in a 35-year-old woman. Anteroposterior pelvic radiograph shows multiple old healed pseudofractures at the right superior and inferior pubic rami, left inferior pubic ramus (arrowheads) and right proximal femur (arrow). The notable feature is the looser zone in the affected medial cortex of the right proximal femur (arrow) which is different from the hypophosphatasia affecting the lateral cortex. (Courtesy of Pramot Tanutit, MD, Songkhla, Thailand)

deformities of the ribs in rickets which are widened and uniformly washed out<sup>(9)</sup>.

The childhood form presents between six months and 13 years of age. The affected patient has

premature loss of dentitious teeth with the incisor teeth usually being the first affected, and associated skeletal deformities including bowed legs, enlarged joints from metaphyseal flaring and a waddling

gait<sup>(1,3,5,7)</sup>. In less severe cases, the radiographical findings may resemble rickets, in that the physes are widened and there is fraying from loss of the zone of provisional calcification<sup>(12,13)</sup> (Fig. 7). The differential diagnosis for metaphyseal irregularity in this age group is metaphyseal chondrodysplasia, type Schmid; however, the zone of provisional calcification is intact<sup>(12)</sup>.

The characteristic finding of the aforementioned "tongue-like" projection from the growth plate into the metaphysis can help to distinguish the childhood form of hypophosphatasia from other forms of rickets or metaphyseal dysplasia. Functional craniosynostosis can also occur in severely-affected young children. Conventional radiographs reveal widened anterior fontanelles due to hypomineralisation, leading to true premature fusion of cranial sutures, resulting in increased intracranial pressure, proptosis, brain damage and the radiographical appearance of "beaten silver skull"<sup>(5)</sup>. Hypercalcaemia and hypercalciuria are frequently present, resulting in nephrocalcinosis and renal compromise.

The adult form usually presents during middle age with pain from a stress fracture in osteomalacia. In the early stage, pain often manifests at the feet from poorly-healing metatarsal stress fractures. Later in the advanced stage, discomfort in the thighs or hips can occur due to femoral pseudofractures that may progress to complete fracture. However, the pseudofractures (looser zone) in such patients mostly affect the lateral cortices of proximal femora, unlike other types of osteomalacia which occur in medial cortices<sup>(5)</sup> (Fig. 8). An increased endogenous level of PPI causes calcium pyrophosphate dehydrate crystal deposition and subsequent degenerated articular cartilage. The patients may suffer from pyrophosphate arthropathy and overt attack arthritis.

In some families with hypophosphatasemia with clinically-mild hypophosphatasia, there are manifestations of calcific periartthritis and ossification of ligaments (syndesmophytes)<sup>(5)</sup>. Odontohypophosphatasia is only diagnosed with dental disease, and is not associated with skeletal abnormality. The last form, pseudohypophosphatasia, shows clinical, radiographical and biochemical findings similar to those of hypophosphatasia, except for normal or increased serum total ALP activity.

Laboratory assays of hypophosphatasia show that total serum ALP is markedly reduced, which is different from rickets or osteomalacia in which the serum ALP is typically increased. It is important to recognise that infants, children and adolescents have one- to two-fold higher levels of ALP than adults. Increased urinary excretion of PEA is supportive of

the diagnosis but it is not pathognomonic. Elevated PLP is a sensitive and specific marker for diagnosis. Serum calcium and phosphate levels are usually increased<sup>(3,5)</sup>.

The prenatal diagnosis of PLH can be reliably made. During the first trimester, mutation of chorionic villi DNAs is analysed by chorionic villus samples. During the second trimester, assay of ALP activity has also proven to be reliable. The prenatal ultrasonographical evaluation is very helpful<sup>(3,5)</sup>. Brons et al studied the appearance of primary ossification centre in the embryos on both radiographs and transabdominal ultrasonography (US) and found that most skeletal structures can be seen on US by the 15th postmenstrual week<sup>(14)</sup>. Routine prenatal US screening for disturbance in foetal development and anomalies should be considered during the second trimester (18-21 weeks). However, in cases of positive family history of disease, evidence of skeletal dysplasia can be already apparent as early as 14 weeks' gestation<sup>(15,16)</sup>.

US assessment of skeletal dysplasia should be able to determine severity and type of limb shortening, degree of mineralisation, possibility of fractures, bone shape, detection of aplasia or hypoplasia of certain bones, evaluation of thoracic dimension, abnormalities of hands and feet, and evaluation of the foetal cranium<sup>(17,18)</sup>. US evaluation of mineralisation is difficult. The degree of mineralisation is assessed by examining acoustic shadow behind the bone and echogenicity of the bone<sup>(18)</sup>. Useful signs of hypomineralisation include an unusually prominent falx, absent or decrease in visualisation of the spine, decreased bone echogenicity and non-uniform or weak acoustic shadow, and ability to visualise both cortices which is not possibly seen in normal bones<sup>(19,20)</sup>.

In classification of short-limbed dwarfs by bone measurement, hypophosphatasia is classified into the severe micromelic group. In this group, the cardiothoracic ratio is increased while the thoracic circumference is decreased. This differentiates it from other dwarfisms in this group, such as thanatophoric dwarfism and homozygous achondroplasia, by decreased mineralisation in hypophosphatasia. The differential diagnosis of short-limbed dwarfism with diffuse demineralisation as revealed in prenatal ultrasonography is osteogenesis imperfecta (OI) type II, hypophosphatasia and achondrogenesis<sup>(20)</sup>.

The US feature in most cases of achondrogenesis is the absence of ossification of spinal column and sacrum. In some cases, hygroma colli or foetal hydrops may also be present. The calvarium in achondrogenesis has better ossification,

in contrast to compressible skull and devoid echogenicity in OI and hypophosphatasia. Fractures of the long bones are not a feature of achondrogenesis<sup>(16,21,22)</sup>. Differentiation between OI type II and hypophosphatasia is difficult. The long bones in OI type II are thickened, while the long bones in hypophosphatasia tend to be thin or may even be absent<sup>(16)</sup>. The major prenatal US features of short-limbed dwarfism, decreased bone echogenicity and thin delicate bone tend to suggest the diagnosis of hypophosphatasia rather than achondrogenesis or OI type II<sup>(16)</sup>.

When hypophosphatasia is confidently diagnosed, the option of pregnancy termination should be provided to the parents due to the extremely poor prognosis<sup>(16,22)</sup>. Currently, there is no efficient medical treatment for hypophosphatasia. Enzyme replacement therapy by intravenous infusion of ALP from other sources has not led to significant clinical improvement. The survival period may be extended by intensive supportive care<sup>(2,3,5,13)</sup>.

#### ABSTRACT

**A two-hour-old female infant presented with respiratory distress and short limbs. Neonatal radiographs showed micromelic dwarfism and generalised demineralisation, especially at the ribs, long bones of both forearms and both fibulae. The spine showed a flattened shape. All long bones showed metaphyseal irregularities and flaring. Normal serum calcium and elevated serum phosphorus were found, while serum alkaline phosphatase was markedly reduced. A diagnosis of perinatal lethal hypophosphatasia was made. The aetiology, clinical manifestations, radiographical findings, laboratory assays, prenatal diagnosis and treatment of hypophosphatasia are discussed.**

**Keywords: bone demineralisation, hypophosphatasia, micromelic dwarfism, perinatal lethal hypophosphatasia, prenatal diagnosis**

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## SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

### Multiple Choice Questions (Code SMJ 200611A)

	True	False
<b>Question 1:</b> Concerning the pathophysiology of hypophosphatasia:		
(a) Tissue-nonspecific ALP (TNSALP) is found in the intestine, placenta and germ cells.	<input type="checkbox"/>	<input type="checkbox"/>
(b) Serum level of tissue-specific ALP is subnormal.	<input type="checkbox"/>	<input type="checkbox"/>
(c) Endogenous content of three phosphocompounds (PPi, PEA, PLP) will accumulate.	<input type="checkbox"/>	<input type="checkbox"/>
(d) High level of PPi in urine and plasma accounts for skeletal demineralisation and calcium deposition disorder.	<input type="checkbox"/>	<input type="checkbox"/>
<b>Question 2:</b> Concerning perinatal (lethal) hypophosphatasia:		
(a) It is a mesomelic type of dwarfism.	<input type="checkbox"/>	<input type="checkbox"/>
(b) Skin-covered osteochondral spurs or Bowdler spurs are seen protruding from the metaphyses of forearms or legs.	<input type="checkbox"/>	<input type="checkbox"/>
(c) Polyhydramnios or blue sclera is never found.	<input type="checkbox"/>	<input type="checkbox"/>
(d) Respiratory distress is from lung hypoplasia and chest deformities.	<input type="checkbox"/>	<input type="checkbox"/>
<b>Question 3:</b> For the radiographical finding in perinatal (lethal) hypophosphatasia:		
(a) If there is calcification in demineralised calvarium, it appears first in parietal and temporal areas.	<input type="checkbox"/>	<input type="checkbox"/>
(b) The posterior elements of spine are more ossified than vertebral bodies.	<input type="checkbox"/>	<input type="checkbox"/>
(c) "Tongue-like" projections which help to differentiate hypophosphatasia from rickets are prominent radiolucent areas of unossified osteoid from the growth plate into the metaphysis.	<input type="checkbox"/>	<input type="checkbox"/>
(d) Clavicles are the least affected by demineralisation.	<input type="checkbox"/>	<input type="checkbox"/>
<b>Question 4:</b> Concerning the laboratory results in hypophosphatasia:		
(a) Infants, children and adolescents have a one- to two-fold higher level of ALP than adults.	<input type="checkbox"/>	<input type="checkbox"/>
(b) Total serum ALP is markedly reduced, similar to rickets and osteomalacia.	<input type="checkbox"/>	<input type="checkbox"/>
(c) Increased urinary excretion of PEA is pathognomonic.	<input type="checkbox"/>	<input type="checkbox"/>
(d) Serum calcium and phosphate levels are usually increased.	<input type="checkbox"/>	<input type="checkbox"/>
<b>Question 5:</b> Concerning the prenatal diagnosis of perinatal (lethal) hypophosphatasia:		
(a) Assay of ALP activity can be analysed during the first trimester.	<input type="checkbox"/>	<input type="checkbox"/>
(b) Evidence of skeletal dysplasia may be already apparent as early as the 14th postmenstrual week.	<input type="checkbox"/>	<input type="checkbox"/>
(c) One of the useful signs of hypomineralisation is visualisation of one cortex of long bones.	<input type="checkbox"/>	<input type="checkbox"/>
(d) The long bones in hypophosphatasia are more thickened bones in comparison with the long bones in OI type II.	<input type="checkbox"/>	<input type="checkbox"/>

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