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Article

Hypophosphatasia: the contribution of imaging

Hypophosphatasie : apport de la radiologie

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Summary
Radiography and imaging are necessary for the diagnosis of hypophosphatasia (HPP) at all stages of life, from the antenatal period to the complications of adulthood, and in the forms of variable severity. The consequences of alkaline phosphatase activity deficiency, namely defective mineralization and bone fragility, may be detected by radiological tools and share features that distinguish them from other diseases responsible for mineralization defects. Radiography and imaging are also fundamental for the screening and diagnosis of the complications of HPP, some of which are related to the episodes of hypercalcemia and hyperphosphatemia (nephrocalcinosis). Radiologists should be aware of the particularities of HPP to efficiently orient the patients toward optimal medical care.

Résumé
La radiographie et l'imagerie sont au cœur du diagnostic de l'hypophosphatasie (HPP) à tous les âges de la vie, de la période anténatale aux complications de l'âge adulte, et dans ses formes de gravité variable. Les manifestations occasionnées par le déficit d'activité de la phosphatase alcaline, déficit de minéralisation, fragilisation de l'os, sont détectables radiologiquement et possèdent des particularités que l'on peut distinguer d'autres pathologies hypominéralisantes. La radiographie et l'imagerie sont aussi fondamentales pour la détection et le diagnostic des complications de l'HPP, certaines liées aux perturbations du métabolisme phosphocalcique (cranioténose « fonctionnelle » de l'HPP, néphrocalcinose). Les radiologues doivent être avertis des particularités du diagnostic d'HPP afin d'orienter efficacement les patients vers une prise en charge optimale.

1. Introduction

HPP is a pleomorphic disease in its clinical presentation. It is also pleomorphic in its radiological presentation. It may be diagnosed at any age using radiological methods in the context of symptoms that vary in terms of presentation, severity and extent.

2. Role of imaging in HPP management

Radiology is a major pillar in both diagnosis and managment of patients affected with HPP. The first symptoms such as lower limb deformities, fractures or rickets, usually trigger an imaging assessment that should lead to the final diagnosis of HPP. The difficulty resides in recognizing the variety of signs, sometimes not specific, that, associated to clinical and laboratory data, suggest the diagnosis of HPP. The difficulty of the radiological diagnosis is proportional to the the age of the patient.

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Following diagnosis, the radiologist is closely involved in patient's monitoring. Depending on the severity of the disease, certain organs require a regular follow-up, such as mineralization of the skeleton, shape of the long bones, growth of the skull, and development of ectopic calcifications – particularly renal calcifications. So far, there is no national or international recommendations regarding the use of imaging for the diagnosis and/or management of HPP.

3. Prenatal diagnosis

The first report of the antenatal signs of HPP was published in 1996 [1]. The earliest signs attributable to HPP were reported at 13 weeks of amenorrhea ([WA]) using ultrasound. They consisted of hydramnios and severe asymmetrical bone abnormalities [2]. Otherwise, the antenatal screening of HPP is done through repeated ultrasound, three-dimensional ultrasound, and/or fetal CT scan from 28-30 WA. Prenatal imaging allow investigation for specific signs of HPP: severe mineralization defect of of the diaphyseal extremities, growth retardation with short long bones, curved long bones, boney spines jutting from the long bones of the arms or legs and covered by skin, fractures, hypoplastic lungs, and severe mineralization defect of the roof of the skull and vertebrae (fig. 1) [3]. In many cases, the thoracic and abdominal circumferences are within the normal limits.

Sometimes the diagnosis is only considered in the third trimester of pregnancy, through ultrasound, when discovering isolated curved long bones, or short long bones or long bones at the lower limit of the normal range. The study by Wenkert et al. of 17 patients diagnosed *in utero* showed that the antenatal radiological signs, even when severe, were not necessarily predictive of the post-natal course. Indeed, 4 fetuses had signs of spontaneous pre- or post-natal improvement [2] [4]. The discovery of these skeletal abnormalities should trigger the discussion of certain differential diagnoses, including Osteogenesis Imperfecta, which is much more common than HPP (Table 1) [5].

4. Radiological diagnosis in infants and children

Some clinical features (Table 2) may trigger standard radiography of the skeleton (neonates) or of long bones (children). The image analysis should address the diagnosis of HPP in the presence of one or several of the signs listed below. Patients share a defective mineralization of both bone and teeth the degree of which varies depending on the severity of the disease.

Overall, the defective bone mineralization is correlated to the alkaline phosphatase (ALP) level. The lower ALP, the greater the bone mineralization defect. Thus, the disease affects the entire

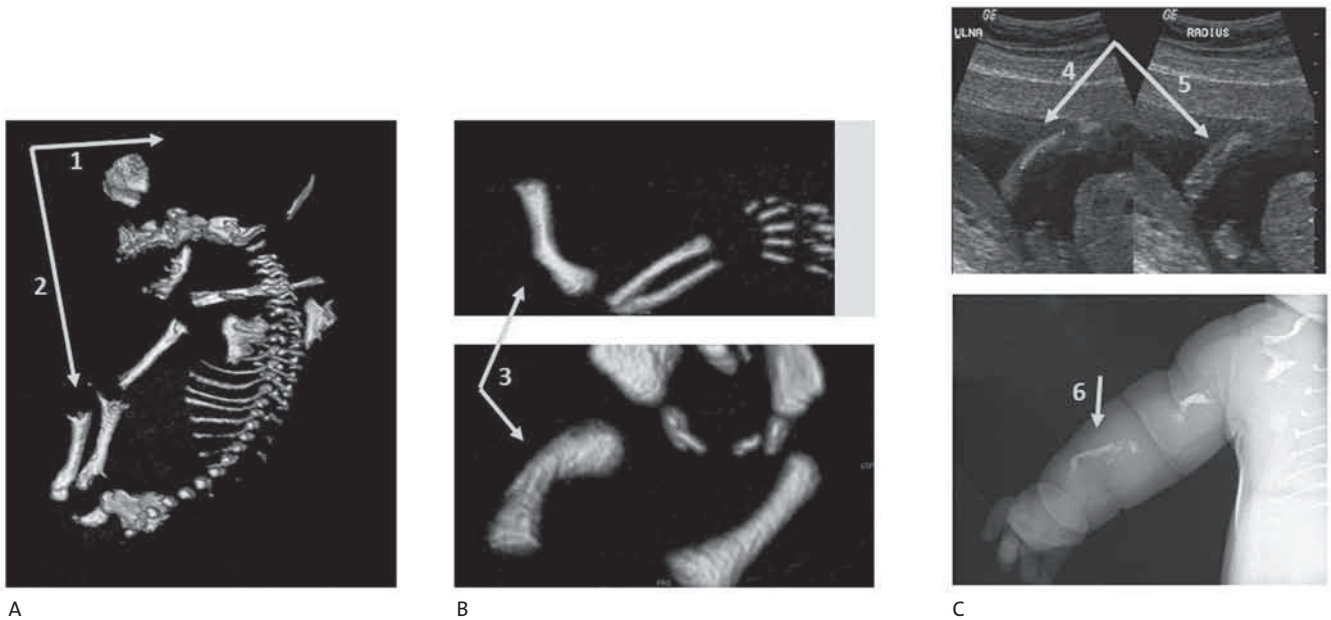

Figure 1. Antenatal imaging of hypophosphatasia.
1A. Fetal CT scan at 32 WA. Note the absence of mineralization of the roof of the skull (arrow 1), thin ribs, and metaphyseal peaks (arrow 2). The infant died of respiratory insufficiency 12 hours after birth.
1B. Fetal CT scan at 32 WA. Curved long bones (arrow 3). Main differential diagnosis: Osteogenesis Imperfecta.
1C. Ultrasound showing radial curving (arrow 4) and fractures (arrow 5) confirmed by postnatal radiography (arrow 6) (severely defective skeletal mineralization), images after [14].