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Chronic intoxication by ethane-1-hydroxy-1,1-diphosphonate (EHDP) in a child with myositis ossificans progressiva

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Abstract. A child with myositis ossificans progressiva was treated for 8 years with ethane-1-hydroxy-1,1-diphosphonate (EHDP) 30–40 mg/kg per day. Latterly he complained of severe, progressive bone and joint pain which made standing and walking almost impossible. A radiographic skeletal survey showed diffuse ricket-like lesions. Withdrawal of EHDP therapy produced substantial improvement in his general condition as well as in the radiographic appearance of the bones. Multiple exostoses were observed in this case and, particularly those around the knees, presented a peculiar morphology. This supports the theory that exostoses originate from a defect of metaphyseal modelling.

Ethane-1-hydroxy-1,1-diphosphonate (EHDP) was the first diphosphonate to be used in clinical practice to inhibit osteoclastic resorption and the process of calcification [1]. In this child with myositis ossificans progressiva it had been administered over a long period to counteract the progressive ossification caused by the disease. The clinical and radiographic evolution of the case illustrate the side effects of this therapy in myositis ossificans progressiva and the care which is necessary when bone remodelling inhibitors are used in children.

Case report

In April 1983, a 5-year-old boy complained of pain in the right knee which was followed by the appearance of a small hard nodule over the lateral aspect of the joint. No congenital or hereditary diseases were present in the family history and no relevant disease had been reported in the first 5 years of life. Shortly afterwards a localized swelling appeared in the right sternocleidomastoid muscle. Initially the lesion was hot and tender, but after a few days the inflammation subsided, leaving a smaller ossified lesion in a retracted muscle. After 5 months the child was found to have torticollis. A muscle biopsy performed elsewhere did not show any relevant pathological change. Treatment with steroid was started and continued for several months.

One and half years later a large soft tissue swelling appeared in the shoulder girdle and followed a course similar to the lesion in the sternocleidomastoid muscle. The child was admitted to another hospital 1 month later. Laboratory tests showed that inflammatory parameters, serum calcium and phosphate, alkaline phosphatase and muscle enzymes were normal. Electromyography was also normal. A muscle biopsy was consistent with myositis ossificans progressiva. Therapy was started with ethane-1-hydroxy-1,1-diphosphonate (EHDP) 30 mg/kg per day. Over the following months new lesions occurred periodically and spread diffusely in the cervical and dorsal regions and sacrum. Limitation of movement developed in the major joints of the limbs, with the exception of the knees.

Two and half years after the appearance of the first signs, diffuse rigidity and widespread calcification of soft tissue were present despite continuous therapy with EHDP. Repeated laboratory tests showed a normal level of alkaline phosphatase. The dose of EHDP was increased to 40 mg/kg per day and low-dose prednisone, piroxicam and androgens were added. Physiotherapy was performed throughout this time in an attempt to prevent joint contractures. In spite of the therapy ossification of muscles, tendons and fascias progressed with increasing limitation of movement and contractures of joints in the following 3 years.

The patient was first admitted to the Paediatric Clinic of the University of Pavia at the age of 13 years, after having taken EHDP continuously for 8 years. Physical examination showed severely reduced mobility of shoulders, elbows, wrists, hips and ankles; the neck was flexed and ankylosed; the dorsal spine had a severe kyphoscoliosis and widespread subcutaneous calcifications were present in the right scapular region. Muscles were diffusely wasted. A short, valgus big toe was present in both feet. The child referred severe pain to joints and bones; walking and standing were almost impossible. The results of routine laboratory tests were normal, as were those on serum muscle enzymes. Bone metabolism parameters were as follows: calcium 9.8 mg/dl [normal range (NR) 9–11]; phosphate 5.0 mg/dl (NR 3–5). Alkaline phosphatase 1942 (increased) fundal examination was normal. Functional tests of respiration revealed severe restrictive changes. Radiography showed frank ricket-like lesions (see below); therefore therapy with diphosphonates was withdrawn.

Two months later the patient's general condition had improved, the pain had disappeared and he could walk without help. Stiffness and joint contractures were unchanged, but the absence of pain had improved his ability in daily activities and he moved more confidently. Results of laboratory tests were as follows: calcium 9.3 mg/dl (NR 9–11); phosphate 6.8 mg/dl (NR 3–5); alkaline phosphatase 1849 (in-

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creased); osteocalcin 36.3 mg/ml (NR 2.0–8.5); vitamin D3 5.2 mg/ml (NR 16.0–74.0); procollagen I > 500 ng/ml (NR 50.0–170.0); procollagen III 200 U/ml (NR 0.3–0.8).

Radiographic findings

Skeletal radiographs performed at different times were available:

1. When the child was 12 years old after 7 years of therapy with diphosphonates
2. At 13 years, when the decision to withdraw therapy was taken
3. Three months after withdrawal of diphosphonates

1. At 12 years epiphyseal and metaphyseal osteopenia of the proximal tibia and distal femur was evident. The growth plate was regular and of normal thickness. A thin denser band was present in the upper part of the metaphysis just below the growth plate (corresponding to the area of primary metaphyseal trabeculae). The proximal tibial metaphyses on the medial side showed bony beaks similar to exostoses; a similar formation was present in the right distal femoral metaphysis. Small exostoses were present on both sides of the left distal femoral metaphysis (Fig. 1 a).

2. At 13 years more severe osteopenia was evident in the growing metaphyses and there was, furthermore, a very broad band of radiolucency (osteoid) between the growth plate and metaphysis such as is usually seen in severe rickets. Within the metaphyseal

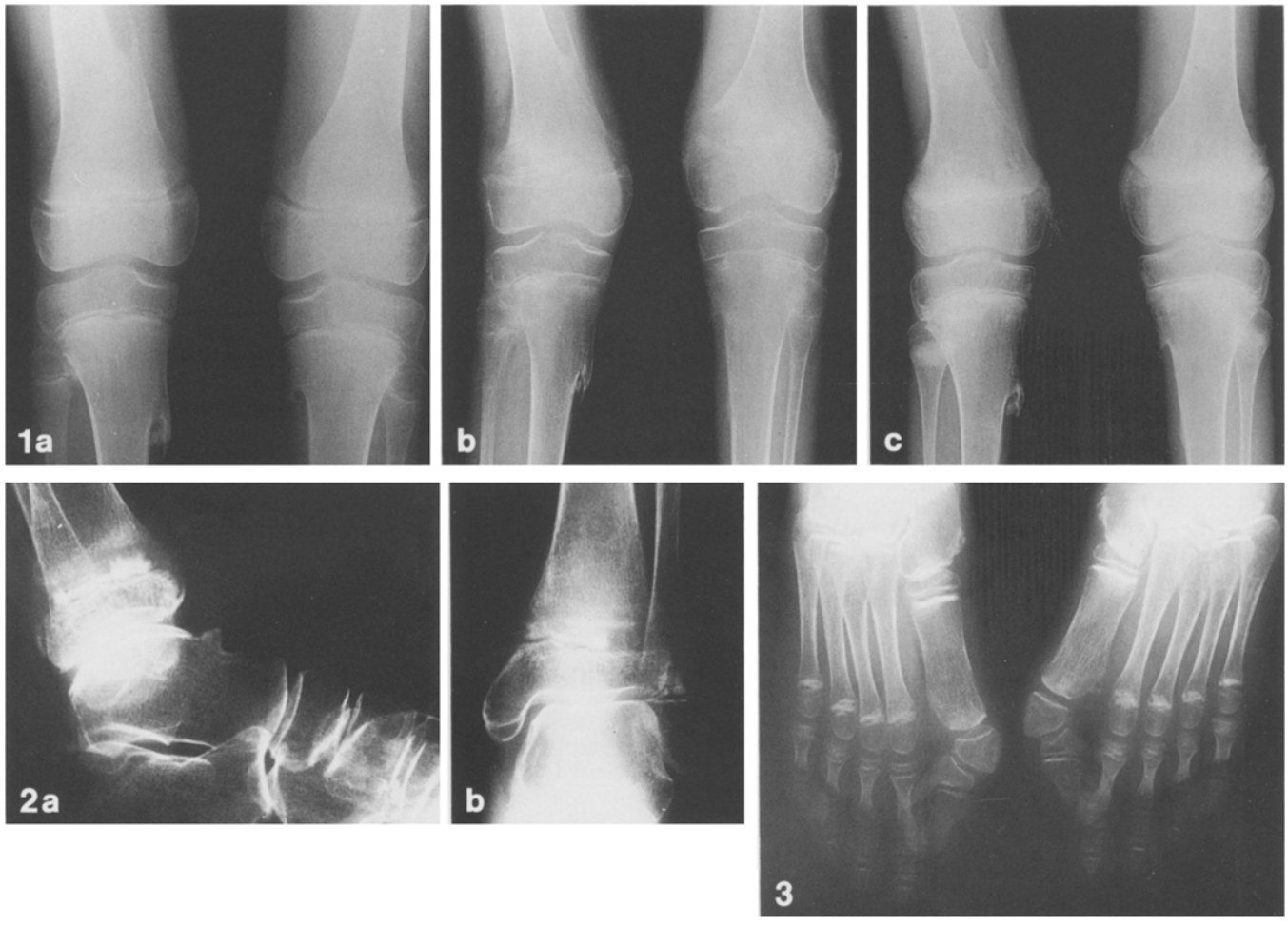

Fig. 1. **a** Radiograph at the age of 12 (after 7 years of EHDP treatment). Note the epiphyseal and metaphyseal osteopenia; denser metaphyseal band at the site of primary metaphyseal trabeculae; exostoses in both tibiae and the right femur; and small exostoses on both sides of the right femur, where coning of the metaphysis starts
b Radiograph at the age of 13 years (after 8 years of EHDP treatment). There is severe osteopenia and a thick, radiolucent band below the growth plate as observed in rickets; the contours of the epiphyses and metaphyses are blurred and irregular; the small exostoses of the right femur are no longer evident
c Radiograph 3 months after withdrawal of EHDP. The metaphyseal radiolucent band has disappeared and there is increased bone density in both epiphyses and metaphyses; in the left femur the two small exostoses have reappeared

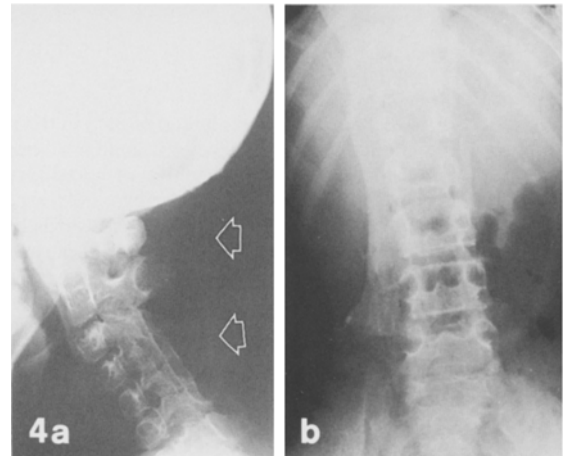

Fig. 2 a, b. Radiographs at the age of 13 years (after 8 years of EHDP treatment). There is osteopenia and ricket-like changes of the distal tibial metaphysis; inside the thick radiolucent band an irregular and dense calcification is present; note the exostosis of the tarsal bone

band of osteoid dense areas of calcification were present (Fig. 1b); the contours of the epiphyseal ossification centres and the borders of the metaphyses were blurred and irregular. Cloaking of tibial and fibular shafts was also evident. Both proximal tibial metaphyses had a cylindrical shape with the lower angle corresponding to the base of the exostoses. The small exostoses in the left femur were no longer evident (Fig. 1b). Similar changes were evident in both proximal metaphyses of the humeri, distal radii, proximal and distal femora, chondrosternal junctions and vertebral end plates; they were not present in the metaphyses of the tubular bones of the hands and feet. Osteopenia was also evident in the shafts of the long bones, the carpal and tarsal bones (Fig. 2) and the epiphyses of long bones. The skull, facial bones, clavicles, ribs and pelvic bones showed mineral density within the normal range. A talar beak was present in both talar bones (Fig. 2). The first metatarsals were short and stubby and the proximal phalanges were divided into two large triangular bones resulting in valgus deviation (Fig. 3). Other findings consistent with myositis ossificans progressiva were the widespread calcification of the nuchal ligament (Fig. 4a), dorsal and lumbar paravertebral muscles (Fig. 4b), and interspinous and intertransverse ligaments of the cervical spine. The apophyseal joints between C2 and C7 were fused (Fig. 4a). The seventh and the eighth left ribs showed a sharp angulation in their second portion and were fused in a large, irregular bony structure abutting below the muscles.

3. At follow-up 3 months after withdrawal of diphosphonates a dramatic disappearance of the metaphyseal osteoid border was evident. In its place bone denser than normal was detectable and the zone of provisional calcification was sharp and well defined. Both proximal tibial epiphyses presented a double bony contour, instead of the blurred and irregular border previously observed. Above the left distal femoral metaphysis the two small exostoses were again evident (Fig. 1c). Osteopenia was also no longer present in the other bones.

Discussion

Skeletal malformations and abnormalities of the big toes are present in 95% of cases of myositis ossificans progressiva [2] and are therefore of great diagnostic value. Four subtypes of malformations of the big toe have been described [3]: those observed in the case reported here fit type 1, but with the peculiar feature (previously unreported) that the single proximal phalanx was divided into two large triangular bones.

EHDP has been used in the treatment of myositis ossificans progressiva to prevent mineralization of areas of active myositis or remineralization after surgical removal of ectopic ossifications [4–6]. Controversial findings regarding the efficacy of this therapy have been reported [2, 7] and variability of results has been ascribed to the activity of the disease and to the plasma level of diphosphonate, which in turn depends on the oral dosage and intestinal absorption [8]. Doses which vary from a minimum of 5 mg/kg per day to a maximum of 40 mg/kg per day have been used [7]. Complications of diphosphonate therapy have been reported by Smith et al. [8] in a boy treated with EHDP 10 mg/kg per day for 2 years and by Rogers et al. [9] in a 3-year-old boy treated with 37 mg/kg per day. The former showed widened growth plates, dense metaphyses and pathological decalcification, while bone pain and muscle weakness were absent. The latter complained of hypotonia, weakness and a shuffling, unsteady gait, and radiographs showed generalized osteopenia, transverse radiolucent bands in the metaphyses of the long bones and widening of the growth plates. Weiss et al. [10], in another patient, documented a decreased bone turnover by radioisotope measurement.

By comparison, other diphosphonates, namely dichloro-methylene diphosphonate and the nitrogen-containing diphosphonates, are known to be potent inhibitors of bone resorption but are less effective inhibitors of mineralization. The effects of the latter on the growing skeleton are band-like metaphyseal sclerosis and concentric epiphyseal and apophyseal sclerosis associated with metaphyseal undertubulation of long bones [11].

Our patient, after a very long period of treatment with 30–40 mg/kg per day EHDP, developed osteopenia, widening of the growth plates and a dense metaphyseal band as reported by Smith et al. [8]. These features progressed to more severe changes of the metaphyses, as described in the case of Rogers et al. [2]. These radiographic lesions were accompanied by weakness, hypotonia and difficulty of gait. There is little doubt that all these are consequences of high-dose EHDP therapy, since withdrawal of therapy was followed by disappearance of all symptoms and normalization of the radiographic appearances.

The variable radiographic features secondary to EHDP treatment can be explained by the mechanism of action of the drug, as shown in animal studies [12]. The dense metaphyseal band, due to arrested resorption of primary metaphyseal trabeculae, together with the cylindrical shape of the proximal tibial metaphyses (failure of conization), indicate an arrest of the remodelling process. This is followed by complete inhibition of calcification, with the transverse band of radiolucency corresponding to accumulation in the metaphyses of a mass of osteoid tissue. The block on calcification is maintained as long as the plasma level of EHDP remains above a threshold value [12]. If this falls, as a consequence of irregularities in the oral intake or intestinal absorption, focal calcification of the osteoid mass occurs, as was evident in our case.

Exostoses were another peculiar feature of our case. It has already been observed that bony beaks, more frequent around the knee, are often associated with myositis ossificans progressiva treated with bone remodelling inhibitors [3]. In the case reported here the multiple exostoses have a peculiar morphology, especially those on the medial side of both tibiae, which supports the view that their formation is due to the arrest of metaphyseal modelling. Moreover radiographic monitoring of the knees after EHDP withdrawal showed the appearance of two small, new exostoses in the left femoral metaphysis where structural anomalies were more severe. This finding supports the theory of the origin of exostoses formulated in a study on multiple exostosis disease [13].

Fig. 3. Radiograph at the age of 13 years (after 8 years of EHDP treatment). Note the dense metaphyseal band of the first metatarsal and the widening of the growth plate; the proximal phalanx is formed by two triangular bones and the toe is deviated in valgus

Fig. 4a, b. Radiographs at the age of 13 years (after 8 years of EHDP treatment). **a** Ossification of the nuchal ligament *(arrows)* and interspinous and intertransverse ligaments of the cervical spine. **b** Ossification of the dorsal and lumbar paravertebral muscles

The osteopenia observed in all the reported cases can be interpreted as osteomalacia and histological confirmation of this interpretation is given by case 3 of Smith et al. [8]. It has been stated that complications of EHDP treatment in growing children are different from rickets [9]. The mechanism of interference of EHDP with vitamin D metabolism remains obscure; however, it cannot be overemphasized that the arrest of bone remodelling and inhibition of calcification are both common aspects of rickets and high-dose EHDP therapy. Moreover the weakness, hypotonia and difficulty of gait present in our case, as well as in that reported by Rogers et al. [9] support the view of a relative disturbance of calcium and phosphate homeostasis.

The results of laboratory tests in our case support the hypothesis of an interference by EHDP with vitamin D metabolism, since the value of the latter was much lower than normal.

The occurrence of these severe complications in children treated for myositis ossificans progressiva casts serious doubt on EHDP therapy. It is not simply a question of overdose, because to prevent mineralization of foci of active myositis it is necessary to reach plasma levels of EHDP at which the active growth plate cartilage and metaphyses are also affected.

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