Acta Orthop. Belg., 2008, **74**, 413-417

CASE REPORT

Anticonvulsant drug-induced rickets and multiple slipped epiphyses in a child treated non-operatively : A case report

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The clinical and radiographic presentation of a child with spastic tetraplegia, anticonvulsant drug-induced rickets, borderline hypothyroidism and multiple slipped epiphyses is described. While the metabolic abnormalities were being treated, the parents denied surgical treatment and have been non-compliant with bracing of the wrist, ankle and knee deformities.

By two years of medical treatment, rickets had resolved and the growth plates of the lower limbs' joints had closed. Non weight-bearing, gentle physiotherapy and bracing led to good results in the hip, ankle and wrist joints and to unacceptable residual valgus angular and rotational deformity of the right knee.

Severely handicapped paediatric patients with metabolic bone disorders, non-compliant with bracing and with co-existent soft tissue contractures, are probably not good candidates for conservative treatment of severe angular limb deformities. However, non-operative treatment of minimal or moderate slippage of the proximal femoral epiphysis (as well as other major epiphyses) can lead to good results.

Keywords : chronic anticonvulsant treatment ; drug-induced rickets ; multiple slipped epiphyses ; conservative treatment.

INTRODUCTION

The purpose of this paper is to describe the case of an 11-year old non-ambulatory boy with spastic tetraplegia, who was diagnosed with multiple slipped epiphyses of the appendicular skeleton, caused by chronic anticonvulsant drug-induced rickets and was treated non-operatively. To our knowledge, no similar case has been reported previously in the literature.

CASE REPORT

An 11-year old boy, with severe non-ambulatory spastic tetraplegia secondary to congenital toxoplasmosis, had been on antiepileptic treatment since the age of 6 months and on triple anti-epileptic medication scheme for the last 5 years. The most recent antiepileptic regime included carbamazepine, lamotrigine and valproate. He was referred

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No benefits or funds were received in support of this study

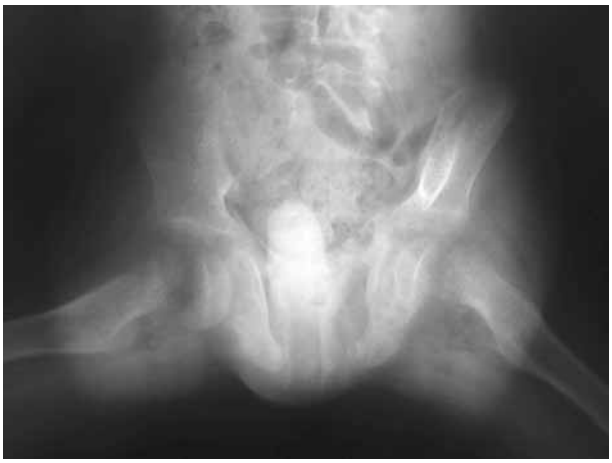

Fig. 1. — Lateral radiograph of the hips at initial presentation

for orthopaedic assessment by the physiotherapist who noted increasing discomfort of the patient during physiotherapy sessions over the last two months. Clinical examination, at that point, revealed painful swelling and reduced active range of movement of all major joints, as well as flexion contractures of the hips and knees, associated with valgus deformity of both knees (more severe on the right side, with co-existent lateral subluxation of the patella), and extension contractures of the right ankle and wrist joints. Radiographs showed generalised dramatic increase in the growth plate height, slipped proximal femoral epiphyses bilaterally, (minimal on the left and minimal to moderate slip on the right side (fig 1), and slipped distal femoral (fig 2), tibial and radial epiphyses (fig 3) on the right side. On the left side, there was no obvious slippage of the distal femoral and distal radial epiphyses, but there was mild posterior slippage of the distal tibial epiphysis. Radiographs of the hips from when the child was 4-years old were available for comparison, with no clear radiographic signs of altered bone metabolism.

Endocrinology work-up revealed vitamin D deficiency rickets, secondary hyperparathyroidism, borderline hypothyroidism, normal pituitary, renal and hepatic function. The child was started on vitamin D_3, calcium and thyroxin supplementation therapy and showed significant clinical improvement with restoration of his biochemical markers to

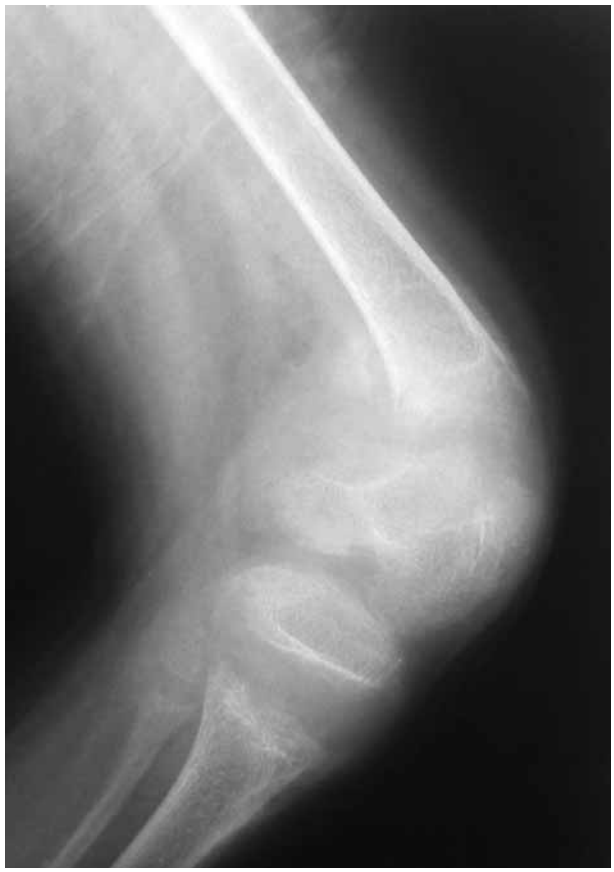

Fig. 2. — Lateral radiograph of the right knee at initial presentation.

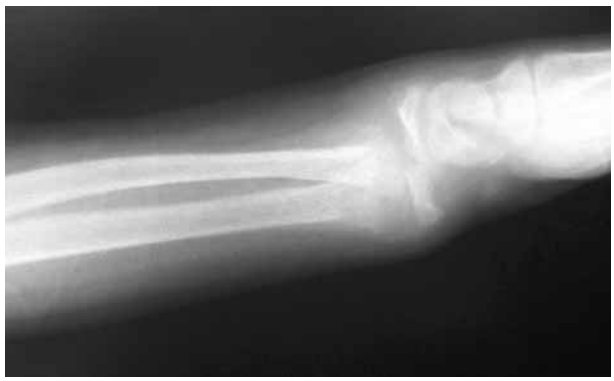

Fig. 3. — Lateral radiograph of the right distal radius at initial presentation.

normal over the following months. At that point, the parents rejected the option of surgical treatment of the slipped epiphyses (mainly the hips). They only

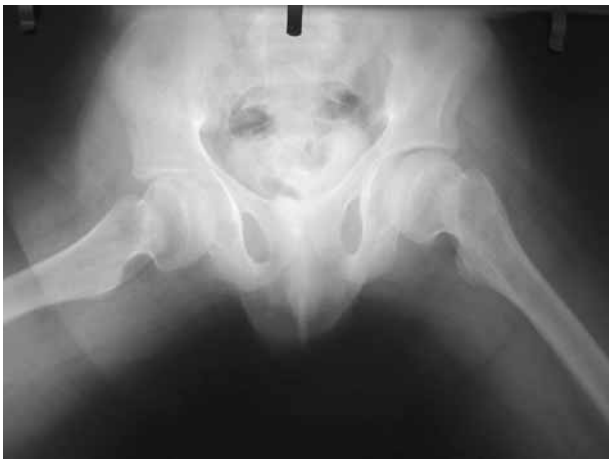

Fig. 4. — Lateral radiograph of the hips after 2 years of medical treatment.

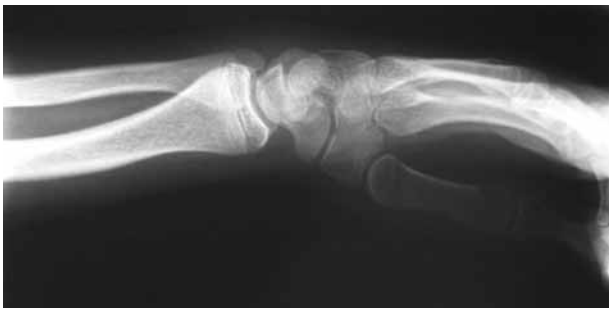

Fig. 5. — Lateral radiograph of the right distal radius after 2 years of medical treatment.

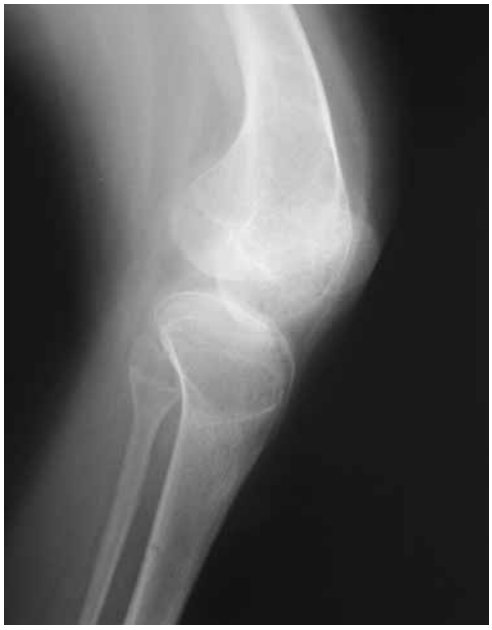

Fig. 6. — Lateral radiograph of the right knee after 2 years of medical treatment.

accepted bracing of the right knee in an effort to improve the severe valgus and flexion knee deformity causing lateral subluxation of the patella. However, the family did not comply fully with bracing instructions, because of the child's discomfort and inability to rest and sleep with it. During medical treatment, the physiotherapist avoided weight-bearing and only active movement was allowed in the hips, along with mild active mobilisation of the knees, ankles and upper limbs.

Orthopaedic follow-up with serial clinical and radiographic examination showed improved and painless active range of movement of all joints with no deterioration of the grade of slippage. At two years of medical treatment, the patient's biochemical markers remained within normal limits and the growth plate of the hips, knees and ankle joints had closed. Good results were observed regarding the configuration of both hip joints (fig 4). On the right side, there was residual mild dorsal angular deformity of the distal radius (fig 5), restoration of the normal alignment of both distal tibial epiphyses and severe valgus angular and mild rotational deformity of the right knee with lateral subluxation of the patella (fig 6).

DISCUSSION

Since the early 1970s, many studies have shown that chronic anticonvulsant treatment can cause rickets or osteomalacia. Several antiepileptic drugs, such as phenytoin and carbamazepine, that induce the hepatic cytochrome P450 enzyme system, can probably affect bone metabolism indirectly by accelerating conversion of vitamin D and its active metabolite, 25-hydroxycholecalciferol, to biologically inactive metabolites (*6,9,18*). More recent studies suggest that all types of anticonvulsant drugs (enzyme inducing and non-inducing) may cause bone loss by multiple mechanisms such as inhibition of proliferation of osteoblast-like cells,

resistance to parathyroid hormone, inhibition of calcitonin secretion, as well as impaired calcium absorption (*5*).

In children, both older and newer antiepileptic drugs, such as carbamazepine, valproate and lamotrigine have been associated with alterations of bone mineralization (*16*). Currently, prophylactic therapy with vitamin D (in doses up to 2000 IU/day) is recommended on initiation of anticonvulsant drug treatment in adults (*4*). For children, existing evidence is limited. Some authors advocated routine prophylactic supplementation with vitamin D, in children treated with the older antiepileptic drugs (such as phenytoin and phenobarbital), while others suggest routine screening for bone mineral density in all patients on antiepileptic treatment, regardless of the type of antiepileptic medication (*16*).

Slipped capital femoral epiphyses have been frequently associated with hormonal and metabolic disorders (*2,3,10,13,15*), but are reported to occur rarely in vitamin D-deficient or vitamin D-resistant rickets (*19*). Mehls *et al* 1975 (*10*) used histological studies to show that the radiolucent zone between the epiphysis and the metaphysic, seen in radiographs in vitamin D deficiency rickets, was caused by accumulation of cartilage and chondro-osteoid, as opposed to the accumulation of woven bone and/or fibrous tissue in renal osteodystrophy. More recent studies confirmed that there is increased width of the hypertrophic zone of the growth plate and defective mineralization in vitamin D deficiency rickets (*12*).

Although conservative treatment (i.e., traction, with or without application of spica cast) of slipped capital femoral epiphyses has been used in the past (*1,2,11,15*), it is currently considered unacceptable, because of the high rate and severity of associated complications, and the prolonged period of immobility and hospitalisation required. However, there are few studies describing good results with non-operative treatment. Jayakumar in 1980 (*8*) reported successful treatment of Grade I slipped capital femoral epiphysis with prolonged non-weightbearing in hypothyroid patients. Swierstra *et al* in 1993 (*17*) described good results with serial casting of distal femoral slipped epiphyses in patients with renal osteodystrophy.

In our case, a number of factors, such as duration of antiepileptic treatment and polytherapy, feeding difficulties, limited physical activity and the presence of severe spasticity of the patient, as well as borderline hypothyroidism, must have determined the severity of the clinical manifestations. Co-existent soft tissue contractures and abnormal posturing must have contributed to the occurrence of slipped epiphyses at specific sites.

Skeletal age measured one year post initiation of medical treatment was 15.5 years (patient's chronological age : 12.5 years), but we did not measure skeletal age at the time of initial diagnosis. Treatment with T_4 may have played a role in accelerated growth and premature maturation of the skeleton. Several studies have shown that thyrotoxicosis in children accelerates growth rate and advances bone age. Thyroxin may exhibit its effect on the growth plate indirectly, through growth hormone (GH) and somatomedins (IGF-I) (*19,12*), but in cell cultures, thyroid hormone was also found to act directly (through thyroid hormone receptors in progenitor cells and immature chondrocytes) to stimulate hypertrophic chondrocyte differentiation and maturation, while inhibiting cell clonal expansion and proliferation (*14*).

Paediatric patients on chronic anticonvulsant treatment with comorbid conditions such as cerebral palsy, which is a powerful predictor for skeletal hypoplasia and osteopenia, should probably be regularly assessed for alterations in bone metabolism and bone mineral density. Conservative treatment, such as non-weightbearing and bracing, may have a role in the treatment of slipped epiphyses in these patients. Soft tissue dynamic or fixed contractures and patient or family non-compliance are relative contraindications to this treatment modality.

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