BISPHOSPHONATE THERAPY IN PEDIATRIC PATIENTS WITH OSTEOGENESIS IMPERFECTA

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ABSTRACT

Osteogenesis imperfecta (OI) is a group of rare inherited disorders of connective tissue with the common feature of excessive fragility of bones caused by mutations in collagen. We present the case of 2 patients diagnosed with different types of OI, both males, one admitted in the neonatal period and one in infancy. The aim of the study was to compare the efficiency of bisphosphonate therapy, following up the quality of life after receiving it, or in the absence of this treatment.

Keywords: osteogenesis imperfecta, bisphosphonates, child

INTRODUCTION

Osteogenesis imperfecta (OI) is a group of rare inherited disorders of connective tissue, mostly inherited as an autosomal dominant disorder, with the common feature of excessive fragility of bones caused by mutations in collagen type I (1), alpha 1 and collagen type I alpha 2 genes, which encode the alpha 1 and the alpha 2 chain of type I procollagen, respectively (2,3). We report 2 patients diagnosed with different types of OI. For the second case we had the possibility to use the bisphosphonate theraphy.

Case 1

A male newborn was admitted in his first day of life to our clinic for bilateral proximal femoral fracture (Fig. 2). He was born naturally, in cranial presentation, at the gestational age of 38 weeks, with a birth weight of 3,200 g, with a good adaptation, uneventful. The pregnancy was not supervised by gynecologist. There was no history of the tendency of fracture in the family and no family history of any baby with fracture at birth. During the hospitalization, the patient presented episodes of nondisplaced spontaneous fractures, after minimal mobilization, which were treated conservatively using the immobilization of the affected segments (Fig. 3): left forearm (Fig. 4), left humerus (Fig. 1), and bilateral shank (Fig. 2). At the clinical and ophthalmological exam, there were observed blue sclera. (Fig. 5)

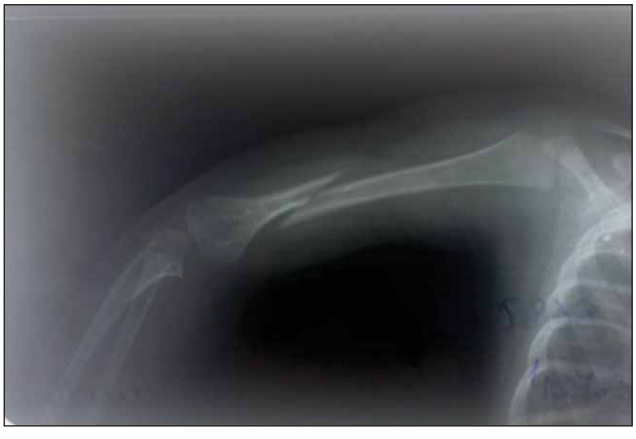

FIGURE 1. *Fracture of left humerus*

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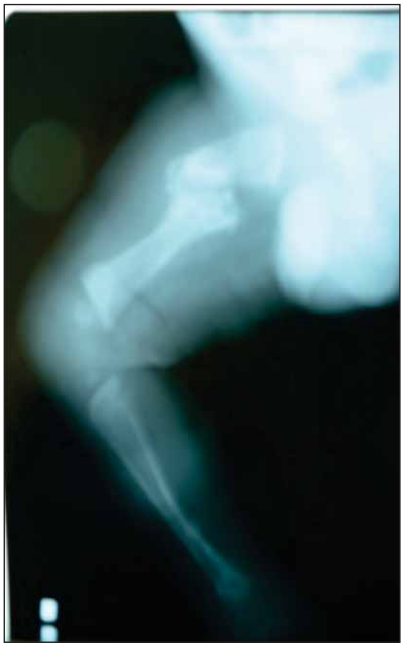

FIGURE 2. *Proximal femoral and shank fracture*

FIGURE 3. *The immobilization of the affected segments*

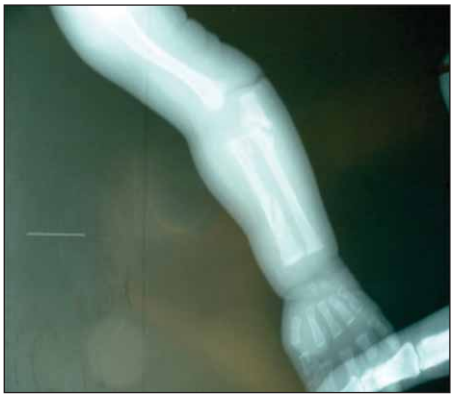

FIGURE 4. *Fracture of left forearm*

Laboratory investigations: total calcium – 7,17 mg/dl (VN: 8,4-11), Ionic calcium – 4,25 mg/dl (4,3-5,3), Phosphorus – 4,29 mg/dl, alkaline phosphatase – 691 U/L(VN: 40-600), creatine phosphokinase – 238 U/L (VN: 24-225), lactic dehydrogenase – 446 U/L (VN:300-600), PTH – 22 pg/ml (15-65) TGP – 18U/L (VN: 5-38), TGO – 46 U/L

FIGURE 5. *Blue sclera*

(5-35), urea – 25 md/d l(VN:10-40), serum creatinine – 0,43 mg/dl (VN:0,4-1,0), urinary excretion of calcium – 65,87 mg/24h (VN: 100-320), urinary excretion of creatinine – 57 mg/dl (VN:90-300), urinary excretion of phosphorus – 290 mg/24h (400-1300), glucose – 88 mg/dl, IgG, IgA, IgM – normal levels, osteocalcin – 28 ng/ml (24-70), 1,25-(OH)2-Vitamin D3 (cholecalciferol) – 45 pg/ml (VN: 29-100), test for lysosomal diseases (Gaucher disease) – negative, the tympanogram, the electrocardiography – normal appareance, the echocardiography – permeable foramen ovale, the osteodensitometry Z score – normal value. The genetic examination confirmed the diagnosis of OI type III. The patient commenced treatment with a regular intake of calcium in addition to a sufficient intake of vitamin D. Until now, at the age of 2 years, the patient had 12 admissions, with a total number of 21 fractures, including 13 femoral fractures, 4 shank fractures, 2 forearm fractures and 2 humeral fractures, mostly iterative, resulting from minimal impacts. During follow up, the X rays showed diffuse skeletal osteoporosis. In this case, the bisphosphonate therapy was not available, and the routine calcium treatment showed little effect. During monitoring, the patient associated rare upper respiratory infections and an episode of urinary infection. In evolution, the patient presented vicious attitude of the affected limb with their deformation in valgum (Fig. 6, 7), functional impotence and compensatory kyphoscoliosis, secondary to lower limb deformities (Fig. 8).

Case 2

A 23 months old male was admitted initial in our orthopedic department for a femoral fracture, after a minor trauma. The anamnesis showed history of two fractures of femur and fibula in the last 8 months, resulting after minimal mobilization,

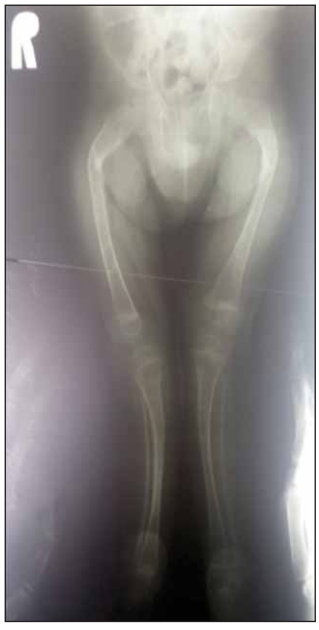

FIGURE 6, 7. *Valgus deformity of the lower limbs*

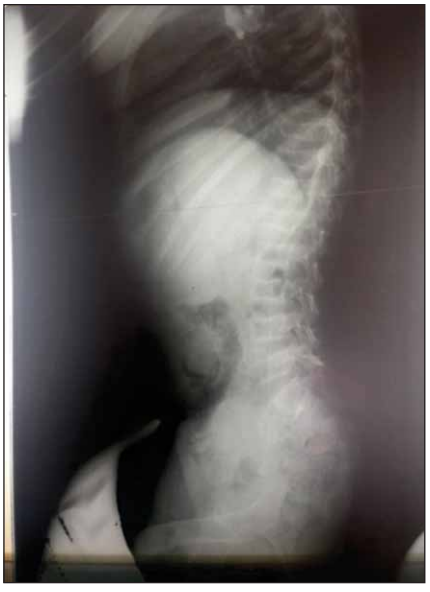

FIGURE 8. *Kyphoscoliosis*

which have raised the suspicion of a bone disease. The clinical exam showed apparently blue sclera (Fig. 11). The patient is the second child of a healthy couple (mother 25yr, father 29yr), with no history in the family of congenital malformation, genetic or reproductive disorders. The pregnancy was supervised, uneventful, and he was born naturally, in cranial presentation, at term, with a weight and length in normal ranges

FIGURE 9. *Apparently blue sclera*

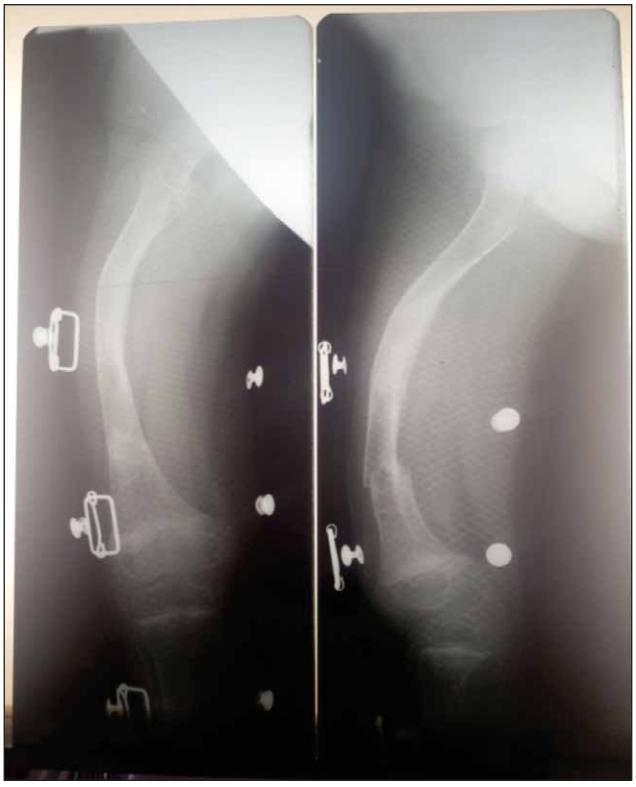

FIGURE 10. *Iterative femur fractures*

FIGURE 11. *Imobilization for femur fracture*

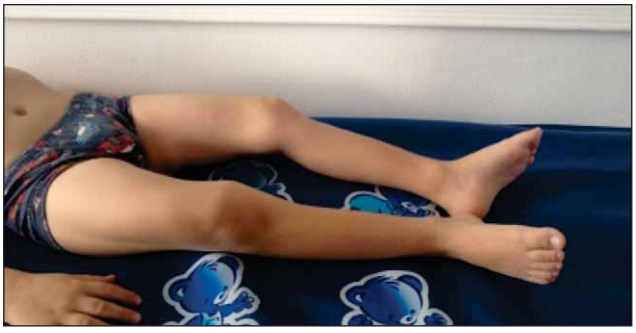

FIGURE 12, 13. *Varus deformity of the legs*

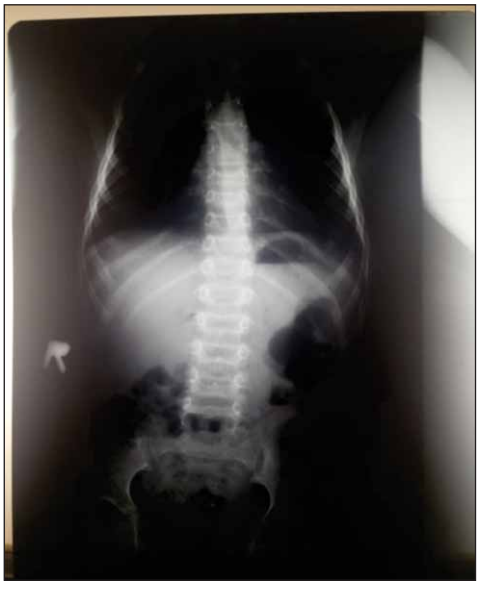

FIGURE14. *Secondary scoliosis*

Laboratory investigations: total calcium – 10,50 mg/dl (VN: 8,4-11), Ionic calcium – 4,56 mg/dl (4,3-5,3), P-4,62 mg/dl, alkaline phosphatase-230 U/L (VN: 40-600), CPK-200 U/L (VN: 24-225), LDH -446 U/L (VN:300-600),PTH-22 pg/ml (15-65), TGP-13 U/L (VN: 5-38), TGO- 22 U/L (5-35), urea – 25 md/dl (VN:10-40), serum creatinine – 0,43 mg/dl (VN:0,4-1,0), urinary excretion of calcium – 35,87 mg/24h (VN: 100-320), urinary excretion of creatinine: 49 mg/dl (VN:90-300), urinary excretion of phosphorus: 283 mg/24h (400-1300), glucose-normal level, IgG, IgA, IgM- normal levels, osteocalcin-25ng/ml (24-70), 1,25-(OH)2-Vitamin D3 (cholecalciferol) – 45 pg/ml (VN: 29-100), test for lysosomal diseases (Gaucher disease) – negative, the tympanogram, the electrocardiography – normal appareance, the echocardiography-ostium secundum atrial septal defect and coarctation of the aorta, the osteodensitometry Z score – 1,7 at lower limbs, Z score at upper limbs – 0.6. The genetic examination confirmed the diagnosis of OI type I. Until now, at the age of 6 years, the patient had a number of total 13 fractures, 12 femoral fractures and one fibula fracture. The osteodensitometric investigation performed at almost 4 years old showed low bone mineral density in the lower limbs with normal values in the upper limbs. During the follow ups, the patient was treated for a period of 2 years (2-4 years) with bisphosphonates, which have increased the bone strength (the osteodensitometric investigation – in normal limits) and reduced to the minimum the rate of fractures as well as prevent deformities of long bones. So during bisphosphonate therapy, fracture rates decreased to 3 vs 7 after stopping the treatment. Growth rate was normal.

DISCUSSION

Osteogenesis imperfecta (OI) is a complex clinical and therapeutic provocation were is characterized by a susceptibility to bone fractures with a severity ranging from slight fracture to prenatal fracture and the abnormal blood coagulation and airway obstruction, cardiovascular anomalies and delayed wound healing (4-7). Physiotherapy, rehabilitation and orthopedic surgery are the mainstays of OI management. The goal of multimodality therapy is to maximize the mobility and functional capabilities of patients (8), and also to obttain a normal quality of life for the patient. Beside the orthopedic treatment and rehabilitation, for the treatment of all types of OI are widely administered (oral or intravenous) bisphosphonates and potent antiresorptive agents (4). Clinical trials have indicated the effectiveness of bisphosphonates in the improvement of bone mineral density and the remission of clinical symptoms (9). Although bisphophonates are not a cure for OI, they provide an effective adjunct to comprehensive care.

Bisphosphonates have evolved over time from its original compound to 2nd and 3rd generation aminobisphosphonates such as pamidronate, alendronate and risedronate (4). In this case, the patient received nerindronic acid, 2 mg/kg, iv, one administration every 3 month, 2 years intervals. Digestive tolerability of oral bisphosphonates is poor and the experience with its use in children is really limited. To facilitate the absorption, which is less than 1% of the administered dose, bisphosphonates must be given in fasting conditions with enough amount of water (10). Currently, there are two pharmacologic options for increasing bone mass. One option involves increasing osteoblastic activity with parathyroid hormone analogue or decreasing osteoclastic activity with bisphosphonates (11). The experience with bisphosphonates in children is limited although there are a growing number of publications showing their usefulness in several bone and metabolic diseases, improving bone mineral density, mobility, incidence of bone fractures and reduced chronic bone pain and biochemical markers of bone resorption in children with OI. Bisphosphonates are generally well tolerated in pediatric patients, adverse effects are limited. In most cases an acute phase reaction is observed with fever, malaise, abdominal pain, vomiting, muscle or bone pain with the initiation of either intravenous or oral agents within 1-3 days, and lasting few days. Asymptomatic hypophosphatemia, hypomagnesaemia and hypocalcemia causing tetany are rare and can be prevented with supplementation with calcium and D vitamin (12). In our case, the treatment was well tolerated, were not detected biological or clinical side effects. Currently in Romania are not available bisphosphonates formulas in pediatric age.

CONCLUSIONS

Combination treatment with bisphosphonates in patients with OI diagnosed at pediatric age is a proven effective treatment option for enhancing the rate of fractures, bone density and the quality of life.

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