RARE CAUSES OF CHILDHOOD OSTEOPOROSIS

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Abstract

Gabriela, 8 years old, was admitted in the 1st Pediatric Clinic, Timisoara for the evaluation of cholestasis syndrome. She was known with hypotonic cerebral palsy, epilepsy with polymorphic seizures partial controlled by anticonvulsants and 5 atraumatic leg fractures occurred in the last 3 years. At admission, she had pale skin, absent subcutaneous tissue and muscle atrophy with muscle atrophy. She had splint cast in the left lower limb and pseudoarthrosis in the 1/3 distal of the right leg. The biological investigations revealed normal liver enzymes except alkaline phosphatase, an abnormal coagulation and bone markers and the presence of starch and fiber in the stool, while the other tests were normal. The radiography of extremities showed osteolysis injuries and old left clavicle, upper third diaphysis of left humerus and femur and lower third diaphysis of right tibia fractures, with vicious callus secondary to Osteogenesis Imperfecta. We considered that all these fractures were manifestations of osteoporosis secondary to malabsorption syndrome, malnutrition, vitamin D and K deficiencies, chronic anticonvulsant therapy and Osteogenesis Imperfecta. The evolution was favorable under treated with calcium gluconate, vitamin D and K with the reduction of alkaline phosphatase and normalization of coagulation. The initiation of bisphosphonate therapy was taken into account. Case particularity: The association of osteoporosis and Osteogenesis Imperfecta responsible for the production of fractures in a patient with cerebral palsy and epilepsy.

Key words: osteoporosis, osteogenesis imperfecta, cerebral palsy

Introduction

For a long period of time, osteoporosis has been considered a health problem specific to postmenopausal women and elderly. According to the medical literature, the incidence of osteoporosis in persons with their age under 50 years old predisposed to developed fracture is increasing up to 30% of women and 13% of men.

Recently, it has been recognized worldwide that osteoporosis could affect also children and adolescents as a primary pathology resulting from intrinsic skeleton abnormalities or as secondary where factors external to the skeleton impair mineralization (various conditions or medications), with ramification that extend during adulthood life. A common presentation of childhood osteoporosis is recurrent long bone fractures, produced by low impact trauma and represents an important cause of morbidity, disability and mortality.

Sometimes, symptomatic osteoporosis may be the first manifestation of an underlying chronic disease such as leukemia or Crohn's disease

Case presentation

The authors want to present the case of Gabriela, 8 years old aged admitted in the 1st Pediatric Clinic of "Louis Turcanu" Children Emergency, Timisoara, in May 2015. She was sent by her general practitioner for a complex evaluation of cholestasis syndrome, which was identified during the routine investigations.

Regarding her personal history, she is the second child of a healthy young family, naturally delivered at the gestational age of 38 weeks with weight of 3550g. The Apgar score was 6 due to a complicated delivery, the patient being reanimated in the delivery room. She has an elder brother with Down syndrome and a healthy younger sister. At the age of 3 month, she had an afebrile seizures treated with Depakine, occasion with whom she was diagnosed with hypotonic cerebral palsy and epilepsy with polymorphic seizures. Also she was known with 5 fractures of the left lower limb (femur and tibia) cured with vicious callus and one fracture of right femur, all these fractured occurred in the last 3 years and were produced without trauma, during her seizures. Her anticonvulsant treatment consistent in high doses of Depakine (500mg/day), Phenytoin (200mg/day), Levetiracetam (700mg/day) and Levomepromazin (6mg/day), which partial controlled these seizures.

At hospital admission, the clinical examination revealed the presence of pale skin, muscle atrophy with muscle contractures and absent subcutaneous tissue. The oral cavity had dental abnormalities. She had a splint cast in the left lower limb and pseudoarthrosis in the 1/3 distal of the right leg, being 3 cm shorter compared with the other extremity, kyphoscoliosis, while the thorax was asymmetric. Cardiopulmonary examination was normal with painless abdomen, with normal liver and spleen size. She has problem with swallow of solid and liquid food, so she was feed by nasogastric tube. The intestinal transit was slow and the diuresis was presented. She was spastic and she didn't speak, sit upright or walk, being immobilized to bed.

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Parameters tested	Value obtained	Normal limit
25OH vitamina D3	16.01 µg /l	20-70 µg /l
Intact parathormon	613.9 pg/ml	15-65 pg/ml
Bone alkaline phosphatase	1174.0 µg/l	36.3 - 159.4 µg /l
B crosslaps	> 6,00 ng/ml	0.566 - 1.690 ng/ml
Osteocalcin	78.86ng/ml	73,0- 206,6 ng/ml

Table 1. Parameters of bone metabolism tested in this patient

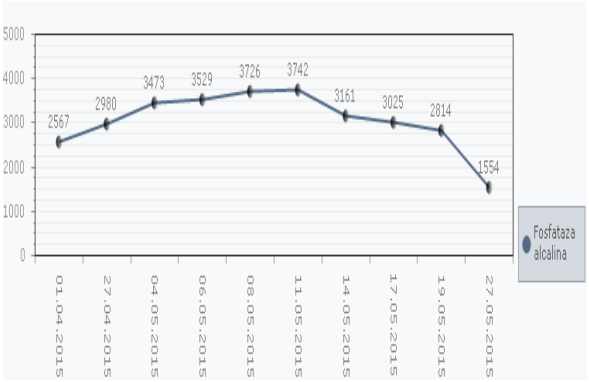

Fig. 1. Evaluation of alkaline phosphatase level under the treatment

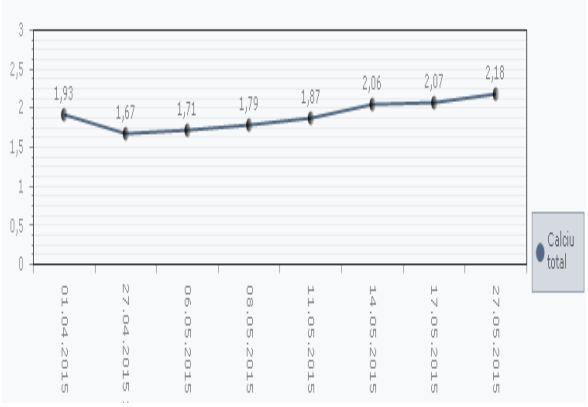

Fig. 2. Evaluation of total calcium level under the treatment prescribed

Anthropometrical parameter were body weight=12kg, body height=103 cm, body mass index=11.32 kg/m2 (under the percentiles of 5 for age and sex).

The biological investigations were complex and were performed on dynamic. The blood tests performed revealed the presence of the iron deficiency anemia, while the other investigations reflecting renal functions, lipid metabolism, proteins, immunoglobulin, and hormones were normal. The evaluation of the cholestasis syndrome consisted in the analysis of the main liver enzymes that were within normal range (TGP=11U/l, TGO=20U/l, GGT=46U/l) except the alkaline phosphatase that was highly increased (2980U/l). These results imposed a detailed phosphor-calcium metabolism evaluation, which underlined decreased value of ionic calcium (0.81mmol/l), total calcium (1.67mmol/l) and phosphorus (0.89 mmol/l). The further investigations regarding the bone metabolism are presented in the table 1.

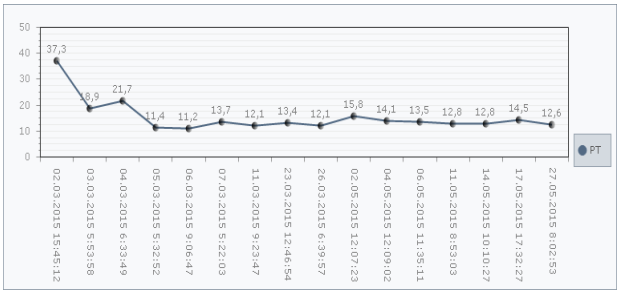

Fig. 3. Evaluation of prothrombim under the treatment with Fitomenandion

The urine examination was normal, while the stool examination identified the presence of starch and fiber in the stool, highly suggestive for malabsorption syndrome.

One day, during the changing of nasogastric tube, Gabriela developed a gastric hemorrhage, fact that imposed the coagulation evaluation which revealed increased values of prothrombin (15,8seconds) and INR- international normalized ratio 1,43 and decreased values of prothrombin activity (55,3%).

The abdominal ultrasound was normal while the radiographies of the superior and inferior limbs showed old left clavicle and upper third diaphysis of left humerus and femur, all cured with vicious callus and lower third diaphysis of right tibia fracture in healing. Also, osteolysis injuries characteristic to Osteogenesis Imperfecta were observed on this investigation. The genetic test for osteogenesis imperfecta is in working.

Based on anamnesis, clinical examinations, biological tests and imagistic investigations, we considered that all these symptomatic and asymptomatic fractures were manifestations of osteoporosis secondary to malabsorption syndrome, malnutrition, vitamin D and K deficiencies, chronic anticonvulsant therapy and Osteogenesis Imperfecta.

The treatment recommended to this patient consisted in the immobilization in splint cast of the right tibia fracture and in prescription of medication address in especially to the vitamin D and K deficiencies and anticonvulsant drugs. So the treatment consisted in the administration of calcium gluconate (100mg/kg/day IV) for 10 days follow by oral micronized calcium (250mg) associated with Vitamin D (increasing doses, from 800 UI/day till 4000UI /day). In parallel, the vitamin K deficit was substituted using Fitomenandion (10mg/day), for 10 days, then orally in

association with other liposolube vitamins. The evolution under this treatment was good with the decrease of the value of alkaline phosphatase till 1500U / l and normalization of the coagulation factors vitamin K dependent, as shown in figures no. 1, 2 and 3.The initiation of bisphosphonate therapy was taken into account

Discussions and conclusions:

Osteoporosis is a systemic disorder produced by the decreased of bone strength, involving low bone mass and microarchitectural deterioration and it predisposes patients to bone fragility and fracture.

In the year 2013, definition of osteoporosis in children was established based on a combination of clinical and radiographic features. According to The International Society for Clinical Densitometry, pediatric osteoporosis can be diagnosed on the basis of a DXA BMD Z-score less than −2 associated with a clinically significant fracture history, defined as: the presence of a) 2 or more long bone fractures by age 10 years or b) 3 or more long bone fractures by age 19 years, or c) vertebral compression fracture.

In our case, unfortunately, DXA (dual-energy X-ray absorptiometry) was not performed, because in children younger than 12 years old, the soft used for the interpretation of DXA results was not adequate. Instead, the increased number of atraumatic fractures in the patient presented stands for this diagnosis. Also, we want to underline the fact, that the performance of DXA in patients with cerebral palsy is a unique challenge because the muscle contractures may prevent patients from lying in the proper position and lumbar spine evaluation may be hindered by scoliosis, the lateral distal femur being an alternate imaging site for these patients.

Based on clinical findings (abnormally of her teethes, kyphoscoliosis, long bone deformities, pseudoartrosis and multiple fractures produced in the last 3 years in absence of trauma) and the radiological aspect of her bones, Gabriela was diagnosed with osteogenesis imperfecta type IV, an important cause of primary osteoporosis in children. There is an underlying abnormality in bone matrix composition, usually due to defective synthesis of type I collagen α chains produced by a mutation in COL1A1 or COL1A2 genes.

One of the most common physical disabilities of childhood, cerebral palsy represents a group of permanent disorders which arise from anomalies in the motor center of the brain due to perinatal infections, asphyxiation, and stroke. It consists in abnormalities of the development of movement and posture associated with disturbances of sensation, cognition, communication and behavior, epilepsy, and secondary musculoskeletal problems. Almost 80% of patients diagnosed with severe cerebral palsy have osteoporosis, with an annual fracture incidence of 4%.

There are a multiple factors which may adversely affect bone density and metabolism in patients diagnosed with cerebral palsy.

The motor disorders of cerebral palsy are often accompanied by immobilization to the bed. In is well known that reduced mobility and muscle load are major cause of reduced bone mass and strength. In this situation, the most common site of fracture in children with reduced mobility is the femur, fact being seen also in the patient presented. In this case, her long bones tend to be slender with thin cortices and reduced trabecular density, and the lower limbs are usually more subjected to trauma from accidents or handling.

Outdoor activities may be significantly diminished in this patient with bone metabolism consequences. So, the limitation of the seasonal sunlight exposure is an important for factor for the serum 25-hydroxy vitamin D level.

In the our patient, oral-motor dysfunctions with swallowing difficulties and feeding by naso-gastric tube are important risk factors for the feeding difficulty, poor nutrition and low calcium, vitamin D and K intakes. All these problems are frequent encountered in patients with such pathology and may contribute to poor mineralization.

The deficit of vitamin K is responsible in the case presented both for abnormality of coagulation factors vitamin K dependent and osteoporosis. The recent researches had shown the role of the vitamin K2 in the activation of osteocalcin – the protein responsible for binding calcium ions to the matrix of bone- and of Matrix Gla Protein protein circulatin implicated in the cartilage and bone metabolism and in reducing the risk of osteoporotic fractures . According to Prabhoo and van Summeren , vitamin K2 is safety and can be used for prevention and treatment in those pathologies known to contribute to osteoporosis.

The treatment of epilepsy in this patient consisted in an association of 4 anticonvulsants in order to control the seizures, which according to the medical literature may adversely affect bone mineralization. Some of them can induced childhood osteoporosis throw the following mechanism such alteration of liver metabolism of 25-OH vitamin D resistance to PTH, inhibition of calcitonin secretion, and impaired calcium absorption or by the direct effects on bone cells.

Many medical studies have shown that under the correct therapy secondary osteoporosis in childhood can be reversible with remission or optimization of the primary causative condition responsible for its development.

There is a complex strategy regarding the treatment of osteoporosis in a patient with cerebral palsy and osteogenesis imperfecta. We initiated the treatment for osteoporosis with an association of calcium and vitamin D and K supplements . According to the medical literature, this association increase bone density by 2% to 10% and decrease the rate of fractures by 35% to 50% . Also mobility and exercise should be encouraged, because of their great beneficial . We take into account bisphosphonate therapy.

Bisphosphonates are the most used medications for the treatment of childhood osteoporosis. They are potent antiresorptive agents that disrupt osteoclastic activity17. In children and adolescents with osteogenesis imperfecta, pamidronate treatment had improve the muscle force, vertebral bone mass and size, bone pain, fracture rate and growth, while in patient with cerebral palsy, biphosphonates had a significant effect on improving bone mineral density

and reduce fragility fractures in children who have a history of fractures.

The treatment with intravenous pamidronate (bisphosphonates) consisted in 0.5mg/kg -first dose followed by 1mg/kg/cycle - next doses over a period of time of 5-6 hours, every 3 months. A cycle is represented by a period of 1-2 days of administration.

In these days, pediatricians have to face new challenges in order to ensure the maintenance of bone health throughout childhood and to provide a strong skeletal foundation for adult life.

The particularity of this case consisted in the presence of a pediatric osteoporosis induced by osteogenesis imperfecta and other causes arise from cerebral palsy deficiencies, responsible for the production of atraumatic fractures.

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