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Clinical Case of Rare Type V Osteogenesis Imperfecta

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Osteogenesis imperfecta, also known as the brittle bone disease, is a clinically heterogenic hereditary connective tissue disease characterized by brittle bones and high risk of skeletal bone fractures. Other observable symptoms, such as deformities of limb and spinal bones, blue sclerae, dentinogenesis imperfecta and progressive hearing loss vary in severity depending on the type of the disease. According to the original classification by D.O. Silence (1979), there are 4 types of osteogenesis imperfecta; however, the number thereof has multiplied due to discovery of new disease-inducing mutations. Type V osteogenesis imperfecta is distinguished by characteristic clinical radiographic symptoms; also, patients with this type of the disease do not feature a type I collagen gene mutation. Nevertheless, all types of osteogenesis imperfecta, including type V, are characterized by high bone brittleness, frequent fractures and further bone deformities, which is the most common cause of incapacitation of the patients.
Keywords: *osteogenesis imperfecta, pseudosarcoma, bone fracture, fibrocartilage callus, densitometry, bisphosphonate, bone brittleness, alphacalcidol, IFITM5, BRIL, children.*

INTRODUCTION

Osteogenesis imperfecta is a clinically heterogenic hereditary connective tissue disease characterized by a predisposition to fractures and deformation of limb and spine bones throughout the whole life. Symptoms such as blue sclerae, short stature, and dentinogenesis imperfecta vary in severity depending on the type of disease.
In 1979, a classification of osteogenesis imperfecta based on clinical radiographic data of 180 patients examined in Australia [1] was proposed. 4 types of the disease were singled out:

- Type I osteogenesis imperfecta (autosomal-dominant mode of inheritance) and is characterized by moderate severity and presence of blue sclerae in the patient;
- Type II osteogenesis imperfecta (perinatal lethal) is divided into subtypes 2A, B, and C on the basis of the X-ray data [2]: extremely severe deformities and shortening of the limbs may be observed in the antenatal period; often – death of respiratory complications;
- Type III osteogenesis imperfecta (progressive deforming) is characterized by significant bone deformations, severe scoliosis;
- Type IV osteogenesis imperfecta (autosomal-dominant mode of inheritance) is characterized by normal sclerae; in contrast with other types, a significant geterogenity is observed in the symptoms [3].

The genetic defect in 90% of cases is mutations in two genes of type I collagen: α1-chains (*COL1A1*) and α2-chains (*COL1A2*)**;** over 1,500 dominant mutations leading to this pathology

(https://oi.gene.le.ac.uk) have been analyzed. However, some patients showed no genetic defects in genes *COL1A1* and *COL1A2*. To date, 17 causative genetic mutations have been identified.
In 2000, Glorieux et al. [3] reported 7 patients diagnosed with type IV osteogenesis imperfecta; however, no blue sclera or dentinogenesis imperfecta were observed along with the typical clinical and histological signs of this type of the disease (ossification of the interosseous membrane, dislocation of the radial head; hyperplastic calluses that occur after a fracture or osteotomy; X-ray tight metaphyseal bands). Histological examination of bone bioptic samples revealed a mesh like lamellar pattern in the bone tissue. Based on this information, it was suggested to single out one other, type V, osteogenesis imperfecta, phenotypically different from other types of the disease primarily in terms of development of hyperplastic calluses. In most cases, inheritance is autosomal-dominant, although not associated with mutations in genes *COL1A1* and *COL1A2*.
Hyperplastic calluses (HPCs) usually develop after a bone fracture or osteotomy; according to some authors, 65% of patients with osteogenesis imperfecta type V develop HPCs, the half whereof are observed in the femur [4]. The youngest age at HPC identification is 9 months. HPC evolution, or the primary growth, may be delayed by several months or several years. After that, HPCs proceed to the stabilization phase; some may become reactivated and grow even more; sometimes the process is reversed with calluses decreasing in size. However, not all patients with this type of osteogenesis imperfecta develop hyperplastic calluses. Not all patients with HPCs develop them after bone fractures and osteotomies: development of calluses may not be preceded by injuries bone fractures. The HPC development mechanism is not completely clear yet; however, according to the histological data, it is assumed that the development of HPCs in soft tissues originates from the periosteal cells [5].
To date, 0 cases of type V osteogenesis imperfecta have been described in Russian scientific literature. Therefore, we present our own clinical observation.

CLINICAL CASE

I., a boy of 7 years and 11 months. Admitted to the medical rehabilitation unit for children with nephrourological diseases, obesity and metabolic disorders of the Research Institute of Preventive Pediatrics and Medical Rehabilitation of the Scientific Center of Children's Health (Federal State Budgetary Research Institution) for the first time.
Medical history: child of the first pregnancy (physiological), first (timely) labor. Age-adequate psychomotor development in the first year of life.
At 10 months of age, the first fracture (of the lower third of the left humerus) due to an inadequate force injury was observed. The next episode followed at the age of 1, when the child started walking: a fracture of the middle third of the left femur. Within the next 4 months, 4 more displaced fractures of different limb segments occurred. Given the repeated fractures of limbs, the child was diagnosed with osteogenesis imperfecta.
From 1.5 to 4 years of age, 10 fractures were observed, mostly in long bones (fractures of femurs, humerus, collarbone and an antebrachial bone), due to inappropriate force injuries. The child was repeatedly admitted for inpatient treatment to trauma departments, underwent metal osteosynthesis several with pins and TEN (titanium elastic nails) several times. Given such characteristic radiographic changes as increase in the bone mass in areas of former bruises (pseudosarcoma), the patient was diagnosed with type V osteogenesis imperfecta.
At the age of 4 years, the patient was prescribed bisphosphonate therapy with pamidronic acid (Pomegara) in the dose of 0.5 mg/kg per day intravenously for 3 consecutive days. After 6 months of therapy, another fracture occurred in the left femur in the middle third with a displacement and fracture of the middle third of the right forearm as a result of falling from the child's own height. Pamidronic acid therapy has been repeated every 4 months (so far, six injections have been administered; the latest one was administered in March 2013), in the setting whereof there has been an increase in bone density, though only in connection with the replacement of bone tissue by a hypertrophic callus (tb. 1).

The latest fracture took place in February 2013; it was a closed fracture of the left femur in the lower third without displacement, after which the child lost the ability to walk unassistedly. As a result of repeated fractures, a large deformation of the axis of the left femur developed. During the last year, the child practiced swimming (2 times per week).
Since April 2013, the patient has been observed at the Scientific Center of Children's Health.
Results of the *hospital examination* characterize the patient's condition as moderately severe. The child's physical development is age-adequate: the patient's weight is 35 kg (97^{th} percentile), the height is 126 cm (50^{th} percentile). SDS (height) is 0.199. BMI – 22. Body position is forced by the deformation of the left femur; unassisted movement is hindered. The thorax has a normal configuration.
Upper limbs: right-hand side varus deformity of the right forearm.
Range of motion in joints: elbow flexion up to 70°, extension – up to 160°. Restricted supination/pronation. Varus deformity of the left forearm. Joint movement not restricted.
Lower limbs: multiplanar deformation of the left thigh (saber, varus, rotary). The left lower limb is in the external rotation position. Range of motion in joints: knee flexion up to 60°, extension – up to 150°. Shortening of the left lower limb by 4.0 cm. Adduction of the left hip restricted. Right lower limb: the axis is not broken, range of motion in the joints is not limited (Fig. 1).
According to the observation and research of *the cardiovascular system, abdomen, kidney and urinary tract,* no pathologies have been found.
According to the X-ray examination of hands, the bone age corresponds to about 7-7.5 years; increased transparency of bone tissue is observed. Thickness of the cortical layer of metacarpal bone II is as follows: T1: 17 mm, T2: 13 mm. Finger width – 57 mm.
Reduction in the serum level of parathormone (5.5 pg/ml at the norm of 8-12) has been observed; levels of total serum calcium (2.56 mmol/l), phosphorus (1.38 mmol/l), alkaline phosphatase (ALP 272 U/L), alkaline phosphatase bone fraction (66.7%), and 25(OH) vitamin D (36,1 ng/ml) are within the normal range (tb. 2).
No increase in renal excretion of calcium and phosphorus was observed: calcium/creatinine ratio: 1.18 mmol/mmol (normal 0.04-0.7); phosphorus/creatinine ratio: 4.5 mmol/mmol (normal 1.2-3.6).
Dual-energy absorption densitometry of the lumbar vertebrae in L2-L4 has not revealed osteoporosis: BMD: 0.742 g/cm^2, Z-score: 0.4.
Audiologist consultation: according to the audiological research, the hearing is normal in both ears.
A *direct sequencing molecular genetic analysis* was performed: c.-14C>T heterozygous mutation was detected in the 5'-UTR region.
Pamidronic acid (Pamidronate Medac) infusion therapy was conducted in the dose of 1 mg/kg per day in combination with calcium (calcium lactate/carbonate, 500 mg per day), and active metabolites of vitamin D (alphacalcidol, 0.5 micrograms per day) for 3 consecutive days. No adverse reactions to drug administration have been observed.

DISCUSSION
In our patient, development of a hyperplastic callus in the left femur due to repeated fractures has been observed. According to the latest X-ray examination of the left femur, pronounced arcuate deformation thereof is observed; the bone is unevenly expanded. Bone structure is heterogeneous; increased bone transparency; multiple cystoid radiolucency. The callus is complete; multiple osteophytes are observed along the posteromedial contour. Heterotopic ossification foci are observed in the adjacent soft tissues (Fig. 2 a, b; 3 a-c).
Development of a hyperplastic callus is usually accompanied by the formation of a hard, painful swelling and fever over the affected areas, elevated over the damaged surface of the bone. In our clinical observation, callus growth was not accompanied by any clinical symptoms; gradual increase in the diameter of the left thigh was observed.
The X-ray picture of a hyperplastic callus may resemble osteosarcoma in connection with the inflammatory component of soft tissues. Observed with computer and magnetic resonance,

hyperplastic calluses are characterized by excessive formation of bone mass and disproportionate size of the affected bone with an extensive expansion beyond the fracture area (Fig. 4).
In any case, differential diagnosis to rule out such diseases as intraosseous osteosarcoma with an aggressive periosteal reaction, periosteal osteosarcoma, juxtacortical myositis and osteochondroma is required.
Given the typical medical history, the presence of multiple fractures, decreased bone mineral density, the X-ray pattern, there is no doubt that this hyperplastic callus developed due to fracture of the femur.
Another characteristic radiographic sign of ossification is the interosseous membrane of the forearm. The cause of this phenomenon may be related to trauma, as well as a hyperplastic callus, but the nature of the formation is not yet fully understood. In our patient, the X-ray studies revealed ossified areas of the interosseous membrane of the forearm bones, so that restricted supination and pronation of the right forearm are observed (Fig. 5).
Congenital dislocation of the radial head is one of the characteristic features of type V osteogenesis imperfecta as well: according to the literature, it is observed in 86% of patients [6]. Bilateral dislocation of the radial head was observed in 88% of patients. As a result, the patients feature restricted pronation/supination of the forearm and reduced angle of flexion. This condition leads to varying degrees of decrease in the patient's functional condition. In some cases, a radial head resection is carried out with the aim of improving the motor function.
Another significant characteristic feature is the X-ray tight metaphyseal bands, which are usually located near the zones of growth (Fig. 6). These bands are clearly contrasted with osteopenic bone areas that become less noticeable with age. Pathogenesis of this feature is not yet clear. It must be differentiated from sclerotic metaphyseal bands that appear during treatment with intravenous bisphosphonates due to the suppression of osteoclastic bone resorption (Fig. 7).
The child, therefore, features radiographic signs characteristic of type V osteogenesis imperfecta; normal color sclerae and no signs of imperfect dentinogenesis are observed.
The genetic nature of the disease remained unclear until 2012, when two independent publications [6, 7] described a heterozygous mutation (c.-14C>T transition) in 19 Korean patients; further, the same mutation was detected in many patients from other countries in the 5'-untranslated region of the gene encoding interferon-induced transmembrane protein 5 (IFITM5), also called BRIL (bonerestricted IFITM-like protein). IFITM5/BRIL membrane protein is exclusively produced in osteoblasts; the highest expression is observed at early stages of the maturation thereof [8]. This protein is most likely involved in bone formation during the embryonic period. Other studies have suggested that IFITM5 protein is involved in the formation not only of bones, but also of the immune system [9, 10]. More precise molecular mechanisms of the BRIL protein are not yet completely understood.
Given all of the above clinical and radiological symptoms observed in the patient, a direct sequencing molecular genetic study was carried out: all the coding exons of gene *IFITM5*, as well as the adjacent intronic region, were examined. In the 5'-UTR region, a c.-14C> T mutation in the heterozygous state was discovered; it leads to the formation of a new start codon and a change in the amino acid sequence of the encoded protein.

CONCLUSION

Osteogenesis imperfecta is to be suspected in a patient with repeated fractures, blue sclerae, bone deformities of limbs, signs of osteoporosis detected by means of X-ray examinations at birth or during the first years of life. Even given this diagnosis, the characteristic radiographic changes of type V disease (hyperplastic calluses degrading the patient's functional condition) are rarely observed in the first year of life. That is why timely detection of symptoms is necessary in order to begin bisphosphonate therapy in time, reduce the risk of fractures and prevent deformation of the limb.
The optimal duration of treatment and frequency of treatment courses are not fully determined; the final conclusions are to be made after further research and accumulation of data. We would also like

to emphasize the need for a multidisciplinary approach to the patients: an interaction of orthopedic surgeons, rehabilitation specialists, pediatricians with the experience of treating patients with osteogenesis imperfecta is required.

Thus, further development of pharmacological and surgical treatment of osteogenesis imperfecta requires creating national and international registries for proper research and evaluation of effectiveness and safety of drugs and methods of surgical treatment.

CONFLICT OF INTEREST

The authors have declared absence of reportable financial support / conflict of interest.

Table 1. Bone mineral density in the setting of bisphosphonate (pamidronic acid) therapy.

Patient's age	Dual-energy absorption densitometry			
	Body weight		Lumbar spine	
	BMD (g/cm^2)	**Z-test (SD)**	**BMD** (g/cm^2)	**Z-test (SD)**
4 years 4 months (09.2010)	0.679	-1.6	0.390	-2.5
5 years 8 months (01.2012)	n/d	n/d	0.495	0.1
6 years 9 months (02.2013)	n/d	-1.0	n/d	+0.6
7 years (05.2014)	n/d	n/d	0.742	-0.4

Note: n/a - not determined, BMD - bone mineral density

Table 2. Biochemical parameters of the patient's blood after one cycle of pamidronic acid therapy.

Biochemical blood examination	Unit	Reference values	Before pamidronic acid infusion	24 h after pamidronic acid infusion
Calcium (total)	mmol/l	2.2-2.7	2.56	2.4
Alkaline phosphatase	U/l	60-400	272	275
Bone fraction of alkaline phosphatase	%	39.3-85.8	66.7	-
Creatinine	mmol/l	27-62	33	30
Urea	mmol/l	1.8-6.4	6	-
Uric acid	mmol/l	119-327	400	-
Phosphorus	mmol/l	1,25-1,78	1.38	1.05
Vitamin D	ng/ml	5.9-59.8	36.1	-
Parathormone	pg/ml	10-65	5.5	33.3

Fig. 1. External examination of lower extremities: increased volume of the left thigh

Fig. 2. X-ray of the left thigh in direct and lateral projections (January 2010)

Note. In October 2009, at the age of 3 years, a fracture occurred in the setting of no adequate trauma; a displaced fracture of the upper and middle third of the left thigh; closed reduction was performed.

Fig. 3. The patient at the age of 6 years (April 2012). Fracture of the upper third of the left thigh due to cycling (without falling)

Note. X-ray of the left femur in the frontal projection: A – TEN osteosynthesis (April 2012); B – May 2012; C – June 2012. All the radiograms reveal a fully-formed hyperplastic callus in the lower third of the left femur as a result of old fractures.

Fig. 4 X-ray of the left thigh (September 2014): AP and lateral projection

Note. The radiogram shows a marked arcuate deformation of the left femur; the bone is unevenly expanded. A heterogeneous bone structure is observed with increased bone transparency and multiple cystoid radiolucency. The callus if completely developed; multiple osteophytes are observed along the posteromedial contour. Heterotopic ossification foci are observed in the adjacent soft tissues.

Fig. 5. Forearm radiography

Note. Arrows indicate ossified areas of the interosseous membrane of both bones of the forearm.

Fig. 6. Femur radiography

Note. X-ray tight metaphyseal bands are indicated with white arrows.

Fig. 7. Right forearm radiography

Note. There are areas of X-ray tight metaphyseal bands (indicated with white arrows): they must be differentiated from sclerotic metaphyseal bands (indicated with black arrows) that appear in the setting of intravenous bisphosphonate treatment due to suppression of osteoclastic bone resorption