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Orthopaedic and somatic status in patients with osteogenesis imperfecta

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Introduction Osteogenesis imperfecta (OI) is a group of rare and relatively diverse genetic disorders, characterized by frequent fractures, bone deformities, low bone mineral density and osteopenia. Frequent fractures, bone deformities, and nonunion are among orthopedic problems in OI patients. Varus deformity of the femoral neck, scoliosis, protrusion of the acetabulum, static deformities of the feet are considered separately. The main goal of surgical treatment of the limb deformities and fractures in OI patients is restoration and maintenance of their motor activity, autonomy and preservation of quality of life in severe OI types. The **purpose** of this study was to assess the deformities in the lower extremities and other accompanying orthopedic disorders, as well as the somatic status of patients with severe OI types (Sillence's types III and IV) at the point of admission to operative orthopedic treatment. Material and methods Between 2003 and 2016, we examined 43 patients with severe OI (types III and IV) which were admitted for operative correction of deformities of the lower and upper extremities, nonunion, and varus deformity of the femoral neck. The average age at the time of admission was 14.4 ± 9.74 years (from 2 years 9 months to 46 years). **Results** Treatment of fractures was conservative in most cases; however, osteosynthesis with wires or flexible nails was used, followed by their removal in 4 patients; bone plates were applied in 4 patients; osteosynthesis with the Ilizarov apparatus was used in 3 cases, and intramedullary osteosynthesis with rigid rods in 4 patients. Regular administration of bisphosphonate preparations was conducted in 9 patients. Last dose of the drug was introduced at least 4 months before admission to surgical treatment. Thirteen patients had undergone reconstructive surgeries on the bones of lower extremities to correct the deformities. **Conclusion** Deformities of the lower limbs in patients with severe OI types are complex and multilevel, which implies the need for multilevel orthopedic interventions to correct them. High incidence of fractures and a complex nature of severe bone deformities result in the loss of the skills to move independently, or even its initial absence. Inadequate surgical interventions, untimely performed, non-telescopic nature of osteosynthesis, and absent bisphosphonate therapy contribute to the formation of additional orthopedic problems and aggravation of the loss of autonomy in such patients, which may complicate subsequent specific orthopedic surgical treatment.
Keywords: osteogenesis imperfecta, limb deformity, stature, weight, body mass index

INTRODUCTION

Osteogenesis imperfecta (OI) is a group of rare and relatively diverse genetic disorders, characterized by frequent fractures, bone deformities, low bone mineral density and osteopenia [1-4]. In most cases, it is caused by a dominant mutation of the genes COL1A1 or COL1A2 [5]. The most widespread OI classification is based on clinical and radiographic manifestations of the disease and distinguishes types I, II, III and IV which have an autosomal dominant type of inheritance [1]. A more complete classification, taking into account the genetic aspects, added type V (dominantly inherited, with formation of bulky hypertrophied bone callus, ossification of interosseous membranes), and types VI, VII and VIII (recessive inheritance) that include patients without disturbances in the synthesis of collagen type 1, but with clinical and roentgenological OI manifestations [3, 4, 6].

Orthopedic problems in OI patients are frequent fractures, bone deformities, and nonunion. Varus deformity of the femoral neck, scoliosis, protrusion of the acetabulum, static foot deformities are distinguished separately [7-9]. Numerous fractures that are accompanied by deformities of the limbs as well as long periods of immobilization and lack of load on the limbs contribute to a decrease in bone mineral density and impair development of child's general motor skills and acquisition of vertical skills, self-service and walking. The overall somatic and functional development of children with severe OI types retards [10-13]. The main goal of surgical treatment of limb deformities and fractures in OI patients is restoration and maintenance of their motor activity, autonomy and preservation of the quality of life in severe OI types [14-18]. It should be understood that surgical orthopedic treatment (reconstructive and/or preventive) should be carried out on many segments of the skeleton, taking into account the systemic nature of the lesion, as well as in patients that suffer from somatic problems.

The purpose of this study was to assess the deformities of the lower extremities and other associated orthopedic disorders as well as the somatic status of patients with severe OI types (Sillence types III and IV) at admission to orthopedic treatment.

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MATERIAL AND METHODS

From 2003 to 2016, we examined 43 patients with severe OI types (types III and IV), who were admitted for operative correction of deformities of the lower and upper extremities, nonunion, varus deformity of the femoral neck. The average age at admission was 14.4 ± 9.74 years (from 2 years 9 months to 46 years).

In addition to clinical orthopedic examination, patients were assessed for independent ability to walk according to the Gillette Functional Assessment Questionnaire Ambulation Scale [19]. Available medical documentation was studied for history of fractures, ways of their management, performance of surgical interventions, therapy with bisphosphonate preparations and mineral density.

The level, location of the apex and deformity angle, presence and position of osteosynthesis implants, location of nonunion and pseudarthrosis as well as the following radiographic and telemetry anatomic parameters of the lower limb segments were studied: mechanical lateral proximal femoral angle (mLPFA), anatomical medial proximal femoral angle (aMPFA), anatomical and mechanical lateral distal femoral angles (aLDFA, mLDFA), anatomical posterior distal femoral angle (aPDFA), mechanical medial proximal tibial angle (mMPTA), anatomical medial proximal tibial angle (aMPTA), mechanical lateral distal tibial angle (mLDTA), anatomical posterior proximal tibial angle (aPPTA), anatomical anterior distal tibial angle (aADTA) [20, 21]. Torsion deformities were assessed by clinical data and, in some cases, with the use of computed tomography (Toshiba Aquilion-64, Japan).

All patients were consulted by pediatricians or therapists before surgery. When assessing the somatic status and concomitant pathology, their medical background, physical examination, standard anthropometric parameters (height, weight, body mass index), laboratory findings, data obtained with additional study methods and results of consultations of specialists were considered.

The obtained quantitative data were subjected to statistical processing using the Microsoft Excel 2016 software. The statistical study included descriptive statistics: mean values (M) and standard deviation (SD).

RESULTS

This study included 43 patients aged from 2 years 9 months to 46 years (mean age, 14.4 ± 9.7 years). Clinical and radiologic OI type III was detected in 14 cases and type IV in 29 patients. The diagnosis was confirmed by molecular genetic studies in 17 patients (type III in 6, type IV in 10, type VIII in 1case). All patients had a history of fractures, at least 5 episodes (the incidence varied from 5 to 100 stances). Treatment of fractures was conservative in most cases; however, osteosynthesis with wires or elastic rods followed by their removal was used in 4 patients, stiff plates in 4 patients, osteosynthesis with the Ilizarov apparatus in 3 cases, and intramedullary osteosynthesis with rigid rods in 4 patients. Nine patients took regularly bisphosphonate preparations. The last dose of the drug was taken at least 4 months before admission. Previously, 13 patients underwent reconstructive surgery on the bones of the lower extremities to correct deformities. The Ilizarov apparatus was used in six patients, intramedullary osteosynthesis with wires or elastic rods in 5 patients. The technique of subperiosteal placement of bone homogenous grafts with their cerclage fixation in one case and in another patient an intramedullary osteosynthesis of the femur and tibia with the Fassier-Duval telescopic system was performed on one side and the Rush rod on the other side.

Of the entire study group, only 4 patients (OI type IV) could move independently within a residential or restricted area without using crutches or walking canes (level 4 in the Gillette Functional Assessment Questionnaire Ambulation Scale); in 13 cases (3 patients of type III, 10 patients of type IV) patients required crutches for movement, but they maintained autonomy (level 3 of the Gillette Functional Assessment Questionnaire Ambulation Scale); in the remaining 26 cases (11 patients of type III, 15 patients of type IV), patients could only move with a wheelchair (level 1 and 2, Gillette Functional Assessment Questionnaire Ambulation Scale). It is important to note that all patients belonging to OI type IV who were treated with bisphosphonate preparations (4 subjects) were able to move independently. Of the five patients with the most severe OI type (type III) who underwent anti-resorption therapy, only two managed to maintain the ability to move with crutches and outside help or with the use of orthotic products. Five patients under the age of 6 years never moved in a vertical position as they did not acquire this skill.

A clinically significant and regularly reported pain with an intensity level 3-4 on the Wong-Baker scale [22] or an analogue scale was reported by 14 patients and was associated with external migration of

intramedullary structures (2 cases), nonunion due to unstable osteosynthesis (4 cases), with axial load on deformed limbs (4 cases), and in the hip or knee joints, lumbar spine by movements (14 patients).

Deformities of the lower limb bones of varying grades were present in all patients (**Fig. 1**). Table 1 shows the types of angular deformities detected at the level of the diaphyseal parts of lower limb bones according to radiographic data. When studying this type of deformities, only cases with a deformity value of 10 or more degrees were considered.

As seen from Table 1, the most frequent deformity was varus antecurvatum in the femur and valgus antecurvatum in the tibia. the angles of orientation of the joint ends relative to the anatomical and mechanical axes of the segments were calculated separately in the patients of this group (Table 2, **Fig. 2**). According to the findings, there were no pronounced disorders in the orientation of the articular ends of the femur and tibia with respect to the anatomical axis of the adjacent diaphyseal parts. On the other hand, clearly pathological angles were observed with respect to the mechanical axes of the segments. This fact indicates that the deformity peak was mainly located at the level of the diaphysis. The true varus deformity of the proximal femur with CORA [20, 21] at the base of the neck or in the intertrochanteric zone was found only in three cases (6 segments). In two cases, this was accompanied by the development of a pathological fracture at a given level (**Fig. 3**). Special attention should be paid to the values of aLDFA lower than the age norm. We believe that these changes are spontaneous adaptive, develop during the growth of the femur, are associated with varus deformity of the diaphyseal part and arise for reducing the medial deviation of the biomechanical axis of the entire limb. Torsion deformities were clinically detected in 67 segments: external femoral torsion of 30° to 90° (46 segments), internal tibial torsion of 20° to 70° (28 segments), external torsion of the tibia from 35° to 50° (3 segments). Deformities were confirmed with computed tomography in 7 cases (**Fig. 4**).

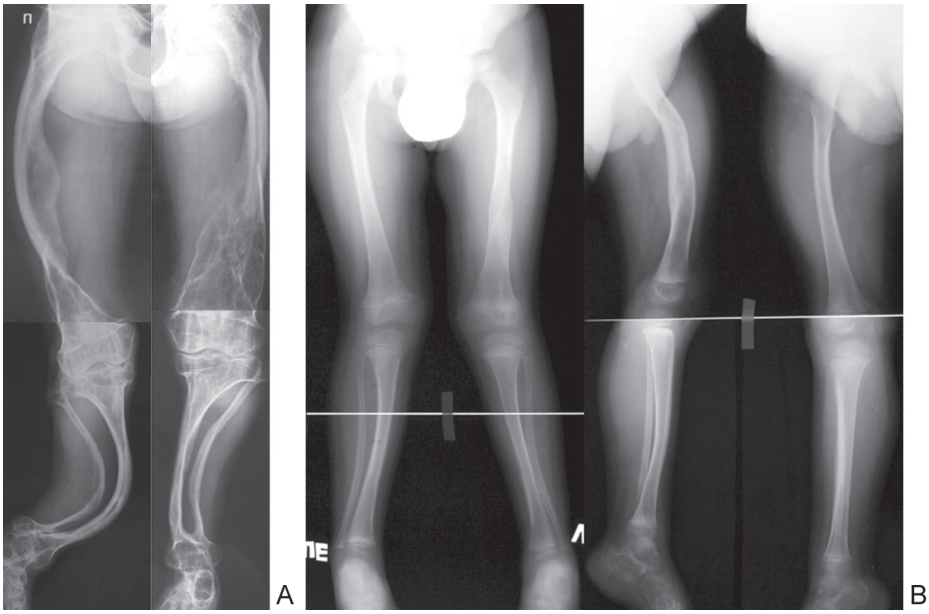

Fig. 1 X-ray telemetry of the lower extremities: A – patient with OI type III, B – with OI type IV

Table 1

Angular deformities of the femur and tibia

Deformity type	Femur (n = 76)	Tibia (n = 76)
Varus antecurvatum (10°–105°)	47	4
Valgus antecurvatum (10°–55°)	3	30
Valgus (10°–50°)	7	11
Antecurvatum (20°–64°)	3	11
Varus recurvatum (25°–42°)	1	1
Varus (10°–35°)	10	–
Valgus recurvatum (28°–35°)	1	1
None	4	18

Table 2

Articular end orientation angles relative anatomical and mechanical axes of segments in patients with varus antecurvatum of the femur and valgus antecurvatum of the tibia

mLPFA	aMPFA	mLDFA	aLDFA	aPDFA	mMPTA	aMPTA	mLDTA	aPPTA	aADTA
74.7 ± 6.9	102.4 ± 9.1	94.9 ± 7.89	78.4 ± 5.9	81.7 ± 10.9	97.7 ± 7.04	84.8 ± 5.3	87.9 ± 7.5	86.8 ± 8.2	85.4 ± 12.9

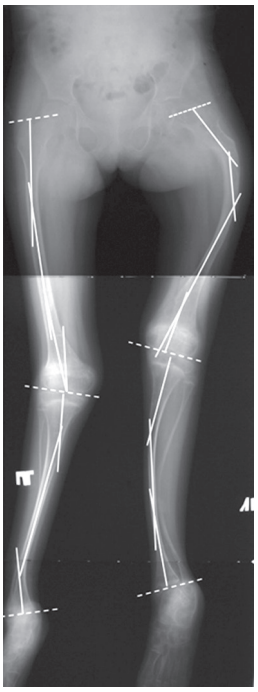

Fig. 2 X-rays of the lower extremities in patient with OI type IV: crossing of solid lines corresponds to the apexes of deformities (CORA), aLDFA: 75° (D), 78° (S)

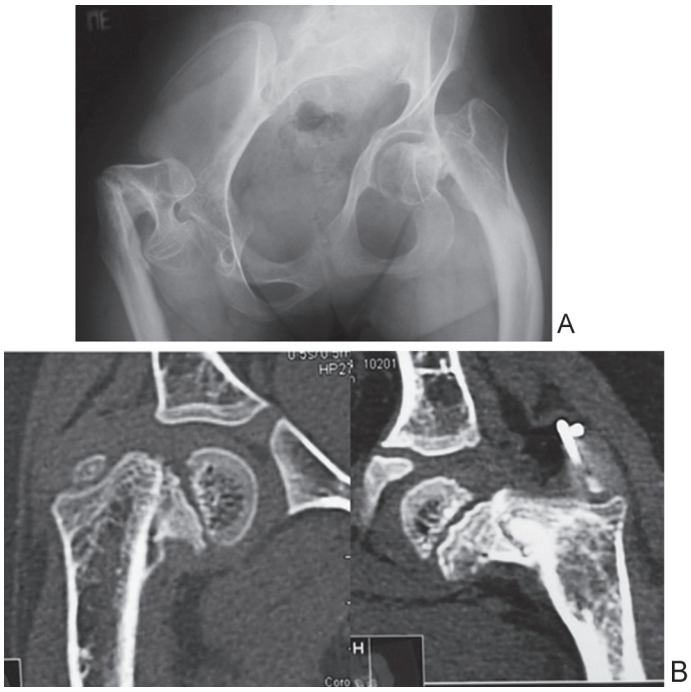

Fig. 3 Nonunions of the proximal femur: A – AP X-ray of the pelvis, B – computed tomography

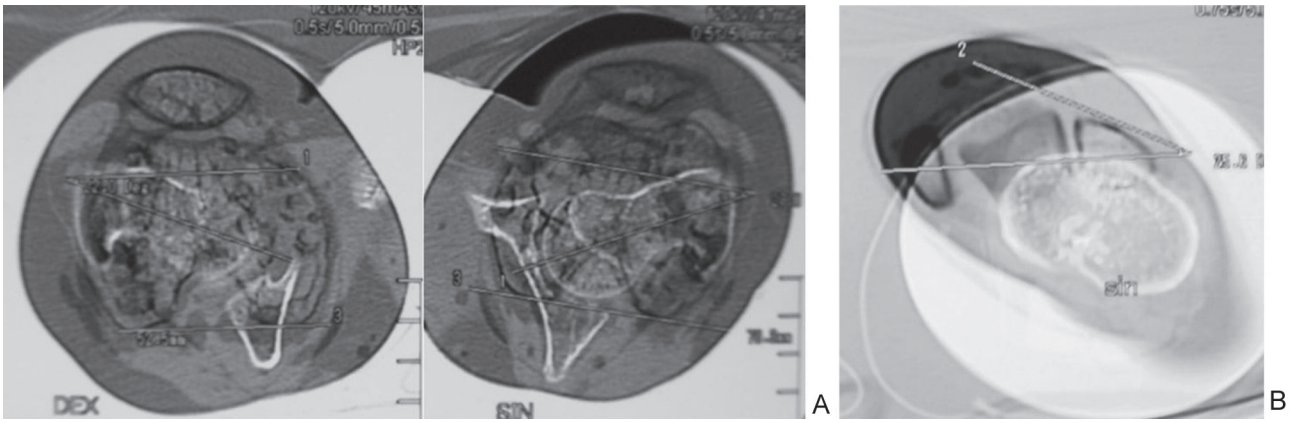

Fig. 4 Torsion deformities, computed tomography: A – retroversion of femoral necks, B – internal torsion of the lower leg bones 35°

Radiographic signs of nonunion (**Fig. 5**), delayed consolidation after fracture, pathological fracture with location of the deformity apex at these levels were: femoral neck (2 segments), upper third of the femur diaphysis (1 segment), border of the upper and middle third of the femur (12), middle third of the femur (6), lower third of the femur (2), middle and lower third of the tibial diaphysis (1 segment).

Various elements of metal osteosynthesis were present in 18 segments (**Fig. 5**): the Fassier-Duval rod with the signs of iatrogenic epiphyseodesis (2), Rush rod (4), plates with the signs of instability (4), intraosseous wires or thin rods (6), cerclage (1), curved or broken rigid intramedullary rod (2).

Among other orthopedic manifestations, scoliotic deformities of varying severity (23°-88°) were present in 13 patients, discrepancy of lower extremities of more than 2 cm in 29 cases, deformities of the upper limbs causing significant functional limitations in 7 cases.

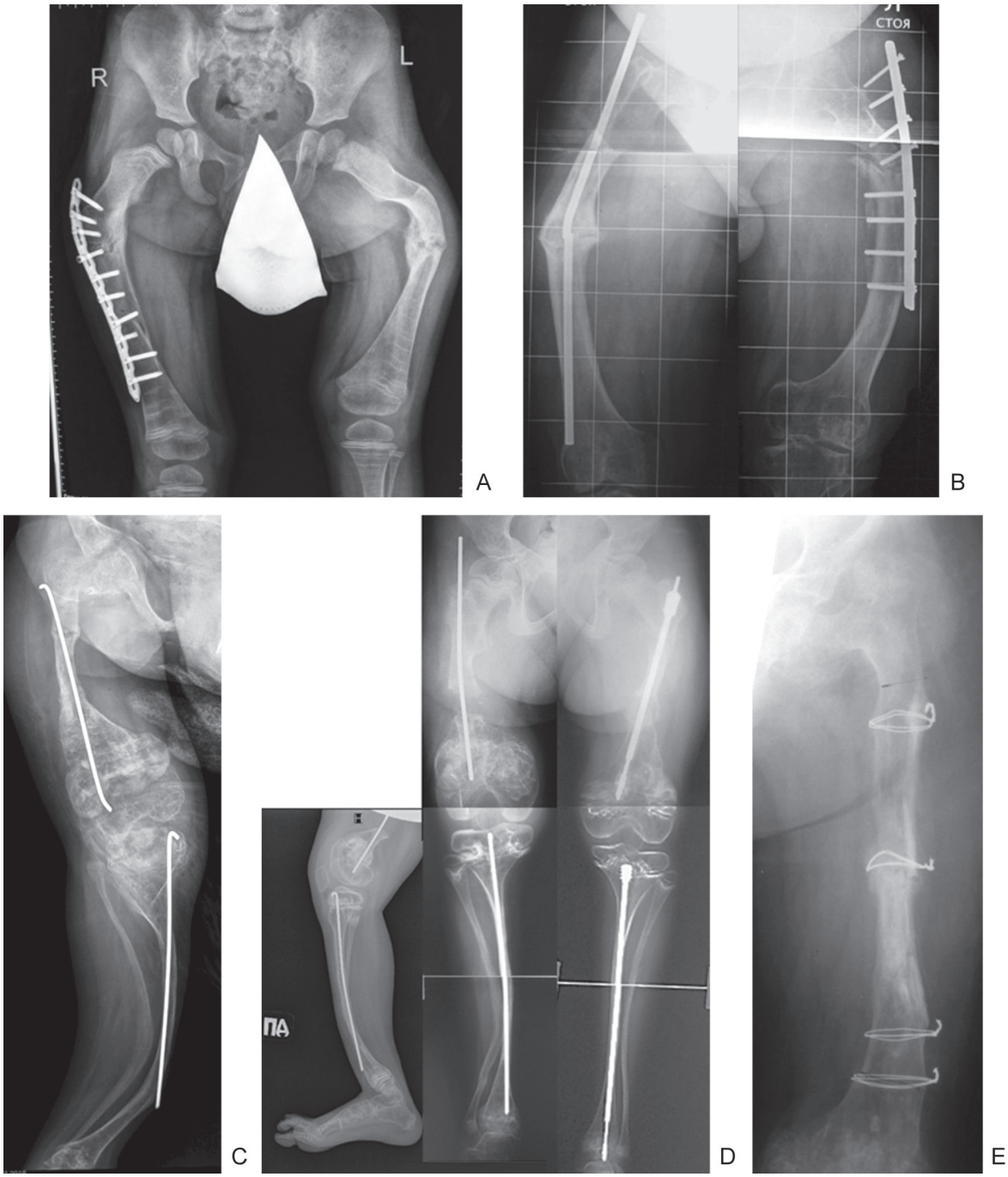

Fig. 5 Examples of nonunion, delayed union, migration of the osteosynthesis material: A – migration of the plate with angular stability, deformity recurrence (right femur), varus deformity, nonunion (left femur); B – pseudarthrosis of both femurs, fracture of the rigid intramedullary rod (right), migration of the plate (left); C – deformity in the presence of intraosseous straight wires; D – telescopic Fassier-Duval rods in the left femur and tibia, non-divergence of rods, distal epiphysiodesis of the femur and proximal one of the tibia, Rush rods in the right femur and tibia, defect-diastasis of the femur, valgus antecurvatum of the tibia; E – cerclage of the left femur, situation 4 years after the subperiosteal placement of autologous grafts, nonunion in the middle third of the femur, coxa vara

The examination of anthropometric parameters detected a pathologically short stature in all patients. Thirty six patients had stature growth below the 5th percentile; four patients had it in the interval from the 5th to10th percentile and three patients from 11th to 25th percentile. BMI lower than the 10th percentile was found in one patient, and BMI corresponding to a level above the 90th percentile in 8 patients, which was accompanied by signs of being overweight and was present in patients aged 3, 9, 13, 14, 16, 37 years . We should note that this conclusion was based on the reference with the weight and stature data in a healthy population.

Mineral density (Z-score) of the lumbar vertebral bodies (L1-L4) ranged from -4.3 to -2.4.

Among the concomitant diseases, chronic upper respiratory tract infections (7), chronic bronchitis (1), vegetovascular dystonia (4), sinus tachycardia (4), arterial hypertension (2), chronic hepatitis (1), chronic gastritis or

gastroduodenitis (3), constipation (12), myopia (6), loss of hearing (7), allergic dermatitis (1), mammary gland fibroadenoma (1), nephroptosis (1), chronic urinary tract infection (3).

DISCUSSION

Decrease in mineralization and mechanical strength of the skeleton bones explains the main orthopedic OI manifestations: fractures and deformities of limb bones, deformities of the skull, vertebra plana in combination with deformities of the spine or without them, flattening of the skull base in combination with progressive compression of stem structures [2, 4, 5, 9, 23]. Due to systemic nature of the damage to connective tissues, frequent OI manifestations are disorders of dentinogenesis, impaired hearing, heart valve failure, chest deformity [2, 4-6]. Frequent fractures, pronounced limb deformities, long periods of immobilization and restrictions in limb loading lead to further reduction of bone mineral density, impaired development of patient's general motor skills, acquisition of verticalization skills and self-service [15-18]. Our study showed that only 17 of 43 patients in group were able to move. Thirteen of them used crutches and orthotic products for verticalization and movement with somebody's help.

The nature of deformities was typical for severe OI types. Varus -antecurvatum deformities in the femur and valgus-antecurvatum of the tibia in combination with pronounced torsion of the segments of the lower limbs were seen in the majority of patients. Other studies describe similar deformities [4, 7, 13, 24]. Our group of patients was characterized by high incidence of nonunion, delayed union after fractures, pathological fractures at the apices of bone deformities. These changes are also a subject for surgical correction, but their prevention is facilitated by timely initiation of bisphosphonate therapy and preventive telescopic nailing [24-28]. In the study group, prior to admission to the RISC for RTO, this combination of treatment methods was not used in none of the cases. It explains, in our opinion, the development of severe deformities of the limbs in combination with nonunion and delayed consolidation. In addition, non-adapted to the mechanical properties of bone tissue methods of osteosynthesis with rigid implants were used in a number of patients, which in all the cases did not lead to the planned treatment outcome (correction of deformities or fracture consolidation), but was accompanied by instability of the implants or even their breaks. It is known that plating is contraindicated in the treatment of OI patients [29, 30].

Thus, the multilevel nature of pronounced deformities of the lower extremities accompanied by significant loss of patients' functional ability and autonomy requiring urgent surgical correction in the group of our patients was associated with absent preventive medical measures (bisphosphonate therapy) and previous inadequate orthopedic surgical treatment. These facts introduced additional complications and elements into the planned surgical treatment.

Somatic problems in patients of our study were frequent, including those OI specific [2, 18, 23, 31]: myopia, loss of hearing, constipation. Concomitant pathology in all cases was compensatory. However, it should be taken into account and required examination by specialists during the treatment course.

Short stature and low body weight (-2 Z-score and even lower than the data for certain ages of healthy children) are typical for patients with severe OI types [32-35]. Given the systemic genetic nature of the disease, it is not possible to use standard anthropometric curves for OI patients. It is known that increased BMI values positively correlate with the frequency of fractures and a decrease in mineral density [36]. High BMI is an unfavorable factor for the preservation of functional abilities in OI patients, reflects a decrease in their motor activity and must be corrected [37, 38]. . Eight patients (18.6 %) in our group had BMI above the 90th percentile.

CONCLUSION

Deformities of the lower extremities in patients with severe OI types are of a complex and multilevel nature, which implies the need for multilevel orthopedic interventions to correct them. High incidence of fractures and a complex character of severe bone deformities result in the loss of the skill to move independently or even its initial inability. Inadequate surgical interventions, untimely performed, non-telescopic nature of osteosynthesis, lack of bisphosphonate therapy contribute to the formation of additional orthopedic problems and aggravate the process of autonomy loss in these patients, which may complicate subsequent specific orthopedic surgical treatment.

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