**INTRODUCTION**

Osteogenesis imperfecta (OI) is a rare heterozygous connective tissue disorder caused by mutations in genes that affect collagen components (in most cases mutations in COL1A1 and COL1A2 genes). The current classification system includes 15 types of OI, one of which (type II) is characterized by 100% intrauterine or perinatal mortality. The structure of mortality in other OI types is poorly understood because of the heterogeneity of clinical symptoms and the severity of connective tissue damage. W present a clinical case of type III osteogenesis imperfecta, complicated by generalized osteoporosis with multiple fractures of vertebrae and tubular bones and progressive kyphoscoliosis. Late-initiated treatment led to progression of the disease and led to cardiopulmonary insufficiency and death of the patient. Our clinical case highlights the importance of timely diagnosis, treatment and regular observation in patients with OI.

**KEYWORDS:** Osteogenesis imperfecta; Osteoporosis; Mortality; Case report
deformations and shortening of the extremities. He required the help of a nurse or relatives for everyday activities.

According to the medical history, OI was suspected at birth. From infancy, the patient was developing disproportionately with gradual formation of kyphoscoliosis and shortening of the limbs, which resulted in inability to walk. Since childhood, patient suffered from partial hearing loss, which progressed with age. At the age of 28 a hearing aid was installed due to bilateral sensorineural hearing loss. Teeth issues also appeared in childhood: opal color of enamel, tooth crumbling. Fractures has been developing regularly since early childhood, with minimal physical impact, 10-12 times a year. Patient felt a «crack» noise at the site of fracture, accompanied by pain, swelling and bruising.

The patient underwent multiple musculoskeletal system assessments in different medical institutions. Nevertheless, he has been refusing to take suggested bisphosphonate treatment for several years because of personal reasons.

During his hospitalization at the Endocrinology Research Centre in 2014, a marked decrease in the lumbar vertebrae BMD (L1-L4 to -4.25D, with maximum decrease in L4 to -6.95D Z-score) was revealed. To assess the number and severity of fractures, as well as the spine and thorax condition, we performed whole-body multispiral computed tomography (MSCT), which revealed multiple vertebrae fractures with pronounced S-shaped right-left scoliosis, shortened long tubular bones, deformities of the pelvical and femoral bones, valgus deformity of the knee joints (Fig. 1). Signs of osteomalacia were most likely caused by vitamin D deficiency, with normal values of phosphorus-calcium metabolism (Table 1). Tubular bones calluses, which could be a confirmation of fractures, were not revealed, which can be explained by the high porosity of the skeleton and the difficulty of CT visualization.

Considering the deformation of the chest, immobilization of the patient, as well as medical history of chronic bronchitis, a cardiovascular system was examined. According to the echocardiography, left ventricular ejection fraction was 57%, the ventricular myocardium wasn’t thickened, the chambers of the heart were not dilated, no zones of myocardium asynergy were presented; signs of diastolic dysfunction of the ventricles and initial pulmonary hypertension were revealed. A cardiologist could not measure the patient’s blood pressure due to pronounced shortening of the extremities, but the the patient did not have left ventricle hypertrophy, it was possible to expect normal blood pressure. Taken together with the sinus rhythm on the ECG, these data suggested that the patient did not have significant cardiac disorders.

Progression of bone deformities, multiple bone fractures, which has been occurring since childhood, marked kyphoscoliosis, barrel chest, impairment of ossification and linear bone growth, as well as the impairment of teeth formation, hearing loss in adulthood - are common clinical features of type III OI. The diagnosis of type III OI was genetically confirmed in December 2014 - a heterozygous mutation c.2260G>T in the COL1A2 gene was found. Another identified heterozygous mutation c.2096G>C in the LEPRE1 gene (the gene is associated with type VIII OI) was probably non-pathogenic.

In order to increase the BMD, decrease the severity of pain in the spinal cord and potentially reduce the risk of new fractures, we recommended the treatment with zoledronic acid 5.0 mg in combination with calcium after correction of severe vitamin D deficiency.

Table 1. Calcium, phosphorus and bone metabolism parameters of the patient I.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calcium (mmol/L)</td>
<td>2,32</td>
<td>2,2-2,55</td>
</tr>
<tr>
<td>Ionized calcium (mmol/L)</td>
<td>1,1</td>
<td>1,03-1,29</td>
</tr>
<tr>
<td>Phosphorus (mmol/L)</td>
<td>1,3</td>
<td>0,74-1,52</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>10,42</td>
<td>15-65</td>
</tr>
<tr>
<td>Vitamin D (ng/mL)</td>
<td>13,2</td>
<td>30-100</td>
</tr>
<tr>
<td>C-terminal telopeptide of type 1 collagen (ng/mL)</td>
<td>0,305</td>
<td>0,01-0,69</td>
</tr>
<tr>
<td>Osteocalcin (ng/mL)</td>
<td>29,96</td>
<td>11-43</td>
</tr>
</tbody>
</table>
During the second hospitalization in Endocrinology Research Centre in November 2016, we noticed that the patient’s condition deteriorated since 2014: he developed paroxysmal productive cough; physical examination revealed an umbilical hernia 8 cm in diameter. After talking to the patient, we found that he did not receive the recommended treatment with zoledronic acid 5.0 mg and calcium; patient was treated only with cholecalciferol in low doses. Whole-body MSCT showed progression of the spine deformity, signs of multiple rib fractures, atelectasis in the left lung S3, signs of infiltrative changes in the left lung 59-10, lower lobe of the right lung, with no change in heart configuration. ECG revealed sinus tachycardia with a heart rate of 102 beats / min; signs of a decreased blood supply to the myocardium in the anteroposterior region and the apex of the left ventricle. Productive paroxysmal cough was considered as a manifestation of chronic pharyngitis, appropriate treatment was prescribed. Patient was previously seen by a surgeon, who recommended surgical treatment for umbilical hernia.

Atraumatic fractures continued to occur regularly 1 time per month, back pain worsened; antiresorptive therapy was strongly recommended. Patient flatly refused suggested infusion of zoledronic acid 5.0 mg. Therefore, denosumab 60 mg injection was administered subcutaneously as an alternative treatment. The patient was discharged, we recommended him to take calcium carbonate 1000 mg / day, cholecalciferol 10,000 IU per week, denosumab 60 mg after 6 months. Considering the change in the configuration and volume of the left lung, as well as signs of right ventricular heart failure, we recommended the patient to visit a pulmonologist.

However, in this clinical case, antiresorptive treatment was administered untimely, after the development of pronounced kyphoscoliosis and the formation of a barrel chest that undoubtedly induced and accelerated the functional degradation of the internal organs and caused cardiopulmonary insufficiency, from which the patient died 6 months after he was discharged from the hospital.

DISCUSSION

McAllion and Peterson analysed 38 cases of death in III OI patients and described life expectancy for this condition and causes of death. According to this study, in most cases death occurred in childhood or adolescence due to respiratory, cardiovascular or post-traumatic complications. The average life expectancy of patients with type III OI was 6.2 years (from 1 year to 28 years) [12].

In England, the structure of OI patients mortality was analyzed based on observations of 743 patients between 1980 and 1993. In the group of patients with type I and IV OI, there was no significant decrease in life expectancy, however, deaths at a young age occurred more often compared to healthy population. In type III OI, there was a very high mortality in childhood, and the risk of death after puberty also significantly exceeded the general population risk [13].

Another large study that estimated life expectancy and causes of death in a cohort of OI patients was based on data from the Danish National Register from 1977 to 2013 [14]. The study included data on 687 patients with different types of OI, and a control group of 3435 people from the healthy population. The average life expectancy in a cohort of OI patients was 72.4 years for men (vs. 81.5 years in the control group) and 77.4 years for women (vs. 84.5 years in the control group). In general, statistical analysis showed that the mortality rate (excluding the cause of death) was 3 times higher in OI group, gender and age matched. Patients with OI had a higher risk of dying from respiratory diseases, gastrointestinal diseases and fractures compared to a healthy population. The study of the register data, however, did not allow separate analysis for each type of OI, therefore the results of the work are averaged, as both mild and severe OI forms were included [14].

Despite different study design, it is obvious that life expectancy in patients with type III OI is much lower than in other non-lethal forms of the disease and compared with a healthy population, which is caused by cardiopulmonary insufficiency at a young age, as well as complications of multiple fractures.

For the last decades, in the world practice, as well as in Russia [7,15], OI patients are being treated with bisphosphonates (BP) from childhood. BP increase BMD by reducing bone resorption, but does not affect collagen fibers. Dwain K, et al. presented an analysis of studies and publications on treatment of OI [1]. Based on the results of this study, BP in OI does contribute to BMD increase, but there is no convincing evidence of fracture risk reduction in this cohort of patients. Moreover, according to the analysis, there is no observed reduction in clinical symptoms (reduction of pain, improvement in bone growth, increased mobility). Thus, the study of the efficacy and safety of prolonged BP therapy requires further study [1].

Besides that, there are attempts to treat OI-induced osteoporosis with drugs with a different mechanism of action [16]. Teriparatide stimulates bone formation and promotes rapid increase in BMD, but its effect on reducing fracture risk in a cohort of patients with OI has not been studied [17-20]. In addition, its use in children is limited due to possible risk of neoplastic process. Denosumab is a human monoclonal antibody with affinity for receptor activator of nuclear factor kappa-B ligand (RANKL) [21]. It has been shown to be effective in the treatment of several children with type VI OI, whereas due to special feature of the pathogenesis, BP treatment did not lead to an increase in BMD [22, 23]. However, there is currently no data on the safety of denosumab in children with OI.

Ideal osteoporosis treatment in OI should focus on increasing bone quality by improving the structural integrity of collagen. For this purpose, studies have been conducted using different in vivo laboratory models for bone marrow and mesenchymal stem cells transplantation for OI patients [22-24]. The first clinical trial included the treatment of OI children with mesenchymal stem cells transplantation from allogeneic bone marrow taken from siblings, which resulted in an increase in growth rate and BMD and a decrease in fracture frequency 6 months after treatment [25, 26]. Thus, the latest medical achievements open new possibilities for the treatment of hereditary bone diseases.

CONCLUSION

The mortality of OI patients is higher than in general population and depends on the severity of connective tissue damage. The majority of deaths are associated with respiratory and cardiovascular diseases, which are primarily the re-
It is necessary to note the importance of an integrated approach to the management ofOI, involving different specialists, including endocrinologists, cardiologists, pulmonologists and surgeons.

**ADDITIONAL INFORMATION**

**The patient’s informed consent.** Official representatives of the patient signed voluntary informational agreement to publish anonymous personal medical data in medical journal Osteoporosis and Bone Diseases.

**Conflict of interests.** Authors declare no explicit and potential conflicts of interests associated with the publication of this article.
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