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Osteogenesis imperfecta type III – a short review and an example of personalized surgery approach

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Abstract

Osteogenesis imperfecta (OI) or brittle bone disease, a heritable disorder of connective tissue, is the most common of the inherited disorders primarily affecting bone. There are approximately 400 individuals with OI in Croatia alone. The basis of this disease in European populations is mostly the result of defects in the structure or processing of collagen type I, an important protein of the extracellular matrix in many tissues. Although fractures occurring with no injury or minor injury are the hallmark of OI, other non-mineralized tissues can be affected as well. Four different types of the disease are commonly distinguished, ranging from a mild condition (type I) to a lethal one (type II). Types III and IV patients present with severe forms. Due to the relatively low prevalence in the general population, treating physicians have limited experience with this disease, both with children or adults. As an example of personalized surgery approach, we present an 11-year-old patient with OI type III. Before referral to our hospital, she was treated with 18 cycles of bisphosphonates as well as with several different surgical procedures. The patient underwent two surgeries at our hospital with a 5-month interval between them. Using the Fassier-Duval intramedullary telescoping nail, correction osteotomies of both femurs and lower legs in two separate settings were performed, with a very good final result.

Keywords: *osteogenesis imperfecta, orthopedics, pediatrics, personalized medicine*

Introduction

Osteogenesis imperfecta (OI) or brittle bone disease is a genetic disorder with varying clinical forms, from those lethal at birth, to mild ones that phenotypically resemble postmenopausal osteoporosis. The disease occurs at a frequency of 6–7/100 000 newborns [1]. Although fractures occurring with no injury or minor injury are the hallmark of OI, other non-mineralized tissues can be affected as well, and the pathological changes can be present in skin, tendons, eyes, teeth and blood vessels. Clinical manifestations are very heterogeneous, and numerous signs and symptoms such as blue sclera, deafness, abnormal teeth development, joint hypermobility, increased risk of hernias, capillary fragility, aneurysms, etc., have been observed. Sillence et al. classified four types of OI based on clinical and genetic findings in patients with OI [2]. Recently, a new classification was published, including 16 different genes responsible for this disease [3]. This diversity calls for a personalized treatment approach. Additionally, if OI patients are treated with early and lasting bisphosphonate therapy and nonelongating fixation implants, they may develop unique long-bone deformities and external/internal bone morphology, therefore, the surgical approach requires a personalized approach as well.

Osteogenesis Imperfecta Type III

Type III OI occurs in approximately 20% of all patients with OI [4]. All infants born with fractures and deformities who survive the perinatal period belong to this group. Most cases are presumably dominant new mutations in both type I collagen genes, however, rare autosomal recessive forms are also possible [5,6]. OI type III is usually recognized at birth because intrauterine fractures produce deformities of the long bones and severe skeletal changes. Clinical manifestations are very heterogeneous and numerous signs and symptoms such as blue sclera, deafness, abnormal teeth development, joint hypermobility, increased risk of hernias, capillary fragility, aneurysms, etc. Most patients have intrauterine

growth retardation, and further progressive growth failure continues during childhood as a result of long bone deformations and spinal involvement. A significant proportion of patients have large and asymmetric heads, while the face is usually triangular. In infancy, sclerae are often pale blue or grey but they regain normal color by puberty. The maxilla is frequently posteriorly inclined, and most craniofacial size measurements are reduced [7]. During the first 10 years of life, the number of fractures and the extent of skeletal changes is approximately the same in type III and type IV of OI. About 30% of patients experience recurrent abdominal pain due to chronic constipation and pelvic deformity with severe acetabular protrusion [8]. Occasionally, congenital cardiac malformations, hemihypertrophy, papillary calcifications or kidney stones, as well as hypercalciuria, are seen [9,10]. The development of all motor milestones is significantly delayed compared with the type I and IV, with a discrepancy between static and dynamic milestones [11]. A child who can sit by the age of nine to ten months is likely to achieve independent walking [12,13]. According to a study by Engelbert et al, 27% of children with OI type III achieved household ambulation with crutches, whereas 45% were restricted to the use of wheelchairs [12]. Most children who are independent in ambulation have poor joint alignment, poor balance, and low endurance. Bending and angulations of the long bones, hip contractures, and pelvic deformities are present in the most severe cases, hindering independent walking. Joint laxity results in hyperextension and valgus position of the knees and feet. Muscle strength is usually severely decreased, with a muscular imbalance around the hip joint [14]. Children who are not ambulatory usually have joint contractures and malalignment of the upper extremities, leading to recurrent fractures [15]. Osteopenia and joint hyperlaxity often lead to progressive kyphoscoliosis and chest wall abnormalities.

At birth, undermineralized calvarium, and elongated long bones and ribs are seen radiologically. Angulation deformities resulting from poor healing often lead to further pathological fractures. Recurrent microfractures of the growth plate appear by the age of two years. They form cystic structures in the epiphyseal region of the long bones (popcorn epiphyses) and arrest growth [16]. Radiographic findings of six or more biconcave vertebrae before puberty is a sign that severe scoliosis is likely to develop [17]. Multiple microfractures of the vertebral bodies lead to further deformities by damaging the vertebral growth plates. Low back pain resulting from vertebral compression fractures following minimal trauma is often experienced. Other complications, such as spondylolysis and spondylolisthesis are also seen. The most severe neurological complications result from the craniocervical instability caused by laxity at the C1-C2 vertebrae. This can lead to the progressive shifting of the tip of the dens of the C2 vertebrae into the foramen magnum resulting in basilar invagination and compression of the medulla oblongata and the cervical part of the spinal medulla. Basilar invagination generally progresses slowly causing many neurological signs and symptoms, which can be very subtle at first [18-20]. The growth rate is severely reduced from birth to about 6-7 years of age and then stops completely [21]. Although severely short stature is almost always seen in type III OI, serum insulin-like growth factor (IGF) I is normal [21,22]. The extent to which the lifestyle of the patient is affected correlates with the severity of the physical impairments. Concerns about physical appearance are intensified in puberty, and depression related to feelings of inadequacy may appear in adulthood [23]. Early mortality in OI type III is due to respiratory illness or complications resulting from basilar invagination or injury. Intracranial hemorrhage can result even from minor trauma and can cause rapid death [19,24].

Case report - personalized surgery approach

To illustrate the importance of a personalized approach to OI treatment, we present the case of an 11-year-old girl, who had multiple surgeries with nonelongating implants during her childhood. At admission, she had a severe angular deformity of both femurs and the lower legs. When she presented to St. Catherine Specialty Hospital, she was unable to walk even with assistance and was confined to a wheelchair. Before admission to our hospital, she was treated with 18 cycles of pamidronate intravenous infusion. Blood sampling was performed before the surgery, and molecular genetic analysis confirmed the clinical diagnosis of OI (type III). The patient underwent two surgeries in our hospital, with a 5-month interval between them. During the first hospitalization, she underwent surgery on both femurs. Firstly, the titanium elastic stable intramedullary nail – ESIN (Nancy) was extracted from the left femur, then a double osteotomy was made of both femurs with fixation by Fassier–Duval telescopic intramedullary nails. Five months after the first hospitalization, the patient was once again admitted to St. Catherine Specialty Hospital for both lower legs surgery. Extraction of two elastic stable intramedullary nailings (Nancy) from the right tibia, double corrective osteotomy of the right and single corrective osteotomy of the left tibia, and fixation of both tibias with intramedullary Fassier–Duval telescopic nails was performed. Figures 1 and 2 show the patient's clinical status preoperatively and ~ 2 months after the second surgery. Radiographs confirmed a good mechanical axis and the correct position of distal threading. Ten weeks after the second surgery, she started to walk with a

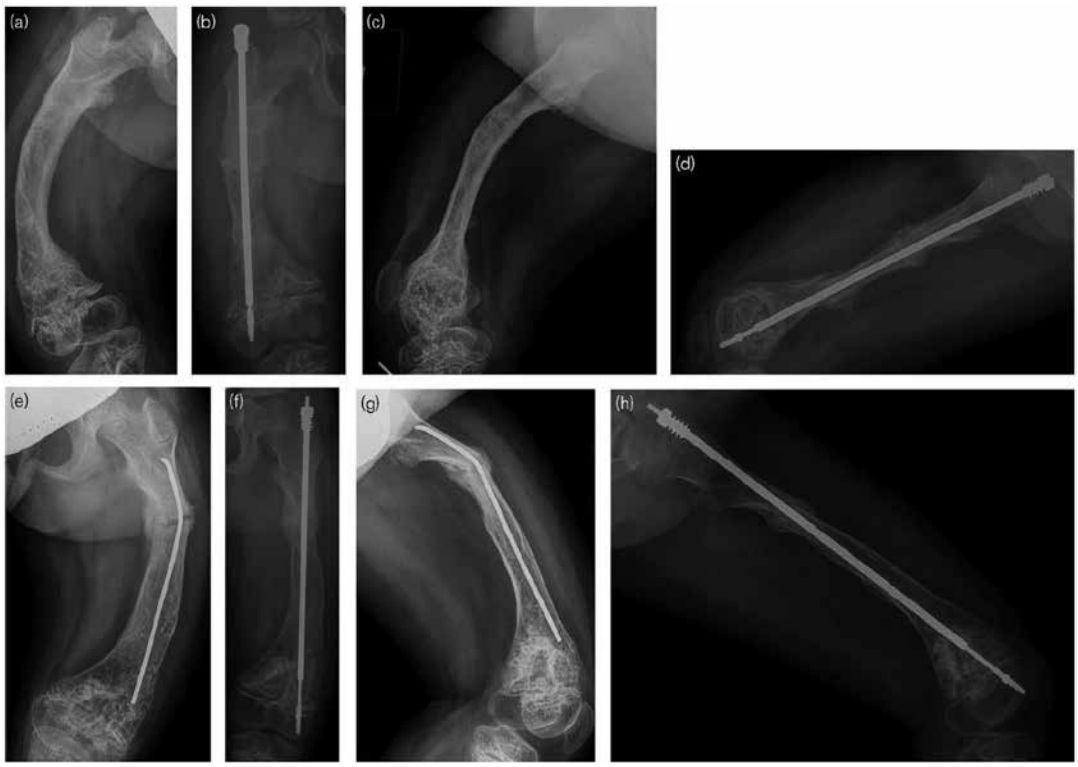

Figure 1. Preoperative and postoperative radiograph of the right femur, anteroposterior view (a, b); preoperative and postoperative radiograph of the right femur, lateral view (c, d); preoperative and postoperative radiograph of the left femur, anteroposterior view (e, f); preoperative and postoperative radiograph of the left femur, lateral view (g, h).

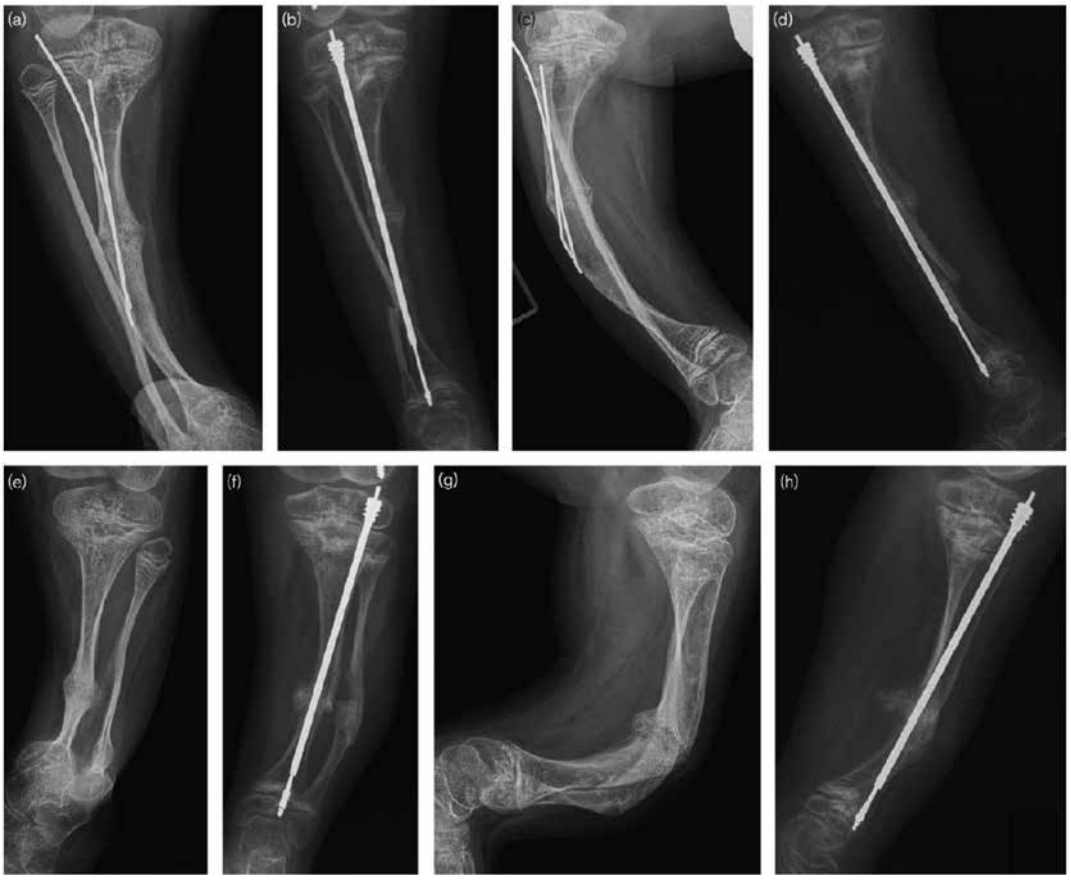

Figure 2. Preoperative and postoperative radiograph of the right tibia, anteroposterior view. (a, b) Preoperative and postoperative radiograph of the right tibia, lateral view (c, d); preoperative and postoperative radiograph of the left tibia, anteroposterior view (e, f); preoperative and postoperative radiograph of the left tibia, lateral view (g, h).

walker on level surfaces, and 5 months after the second surgery, she was able to walk with crutches. Finally, 7 months after surgery, she walked independently or sometimes with crutches, and she is able to climb the stairs. A 2-year follow-up revealed no changes in the patient's status.

Discussion

Due to a plethora of clinical and genetic classifications with many types and subtypes of OI, it is not possible to make a single algorithm of treatment and a universal approach, which could be useful and successful for every patient. It is very important to take into consideration every patient individually and to make a particular plan of treatment for every single patient. The cornerstone of OI treatment in St Catherine Specialty Hospital is a personalized approach to every patient. Molecular analysis of our OI patient was performed before the surgery, and it confirmed the clinical diagnosis – OI type III. The molecular genetic analysis helps to understand general aspects of the disease and has a strong predictive value on the final therapeutic outcome. It has been suggested that the mutations closer to the carboxy-terminal end of the triple-helical domain, including glycine substitution, lead to more clinically severe OI than those towards the N-terminus [25]. Nevertheless, mutations positioned at the C-terminal end of the alpha2 chain are not only related to limb anomalies but also to intracranial hemorrhage [26]. During the surgery, there are three key points and goals: correction of the angular deformity, preparation of intramedullary canal and preparation of soft tissue. The patient who was presented is an example of a severe OI case. Angular deformities of her thighs and lower legs were very severe and, before admission to our hospital, she was treated with 18 cycles of intravenous infusions of pamidronate. Because of repeated treatment with antiresorptive therapy, the remodelation of her bones was slowed down, and the intramedullary canal was filled with sclerotic bone. The sclerotic intramedullary canal makes it very difficult to pass the narrow or obliterated sites of the diaphyseal bone. This can extend the duration of surgery and also lead to other complications including perforation of the bone cortex, malposition of the distal threading and increased blood loss. Preoperative radiographs presented that every segment was deformed in two different directions: procurvatum and varus. As a result, we obtained a new unique deformity of each bone, which required careful preoperative planning of the osteotomy level and the size/angle of the excised bone wedge. All of the presented deformities may look similar but it is impossible to find two exactly the same. Every segment required a personalized approach: preoperative planning, patient positioning on the operating table and, last but not the least, correction of the deformity. The case we presented represents an illustrative example of our approach to the treatment of severe forms of OI. However, we expect that the efficiency of our treatment concept will be confirmed during a longer follow-up study of all OI patients treated in St. Catherine Specialty Hospital.

Note:

Osteogenesis imperfecta type III – a short review and an example of personalized surgery approach is an excerpt from the texts prepared for: Journal of Pediatric Orthopaedics, scientific journal (Jeleč Ž, Primorac D, Antičević D. Personalized surgery approach in severe form of osteogenesis imperfecta type III: point of view. J Pediatr Orthop B. 2019 Sep;28(5):505-508. doi: 10.1097/BPB.0000000000000598.) in which a point of view for personalized surgery of osteogenesis imperfecta patients was introduced; and Croatian Medical Journal, scientific journal (Primorac D, Rowe DW, Mottes M, Barisić I, Anticević D, Mirandola S, Gomez Lira M, Kalajzić I, Kusec V, Glorieux FH. Osteogenesis imperfecta at the beginning of bone and joint decade. Croat Med J. 2001;42(4):393-415.), in which a comprehensive review of the disease was published.

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