Osteogenesis imperfecta (OI) is a genetic disorder characterized by fragile bones. It is our aim to illustrate variability in clinical presentation of severe form of OI. As an example of personalized surgery approach we present an 11-year-old girl with OI type III. Prior to referral to our hospital, she was treated with 18 cycles of bisphosphonates as well as with several different surgical procedures. Due to no improvement in her mobility status she underwent two additional surgeries at our hospital with a 5-month interval between them. Prior to the surgery, molecular genetic analysis was performed and the clinical diagnosis of OI was confirmed. Using the Fassier-Duval intramedullary telescoping nail, we performed correction osteotomies of both femurs and lower legs in two separate settings, with a very good final result. According to our experience, the Fassier–Duval nailing system is a good option, but one should pay attention to many details while performing surgery. Thus, making treatment of OI patients very personalized. In this paper we present a unique personalized approach in OI: firstly, diagnosing COL1A1 gene mutations and secondly, performing a complex two-part surgery. J Pediatr Orthop B 28:505–508

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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]. 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. In 1979, Sillence et al. [2] proposed a numerical classification of OI into four types on the basis of clinical and genetic findings in patients with OI. Since then, there were a few changes and extensions of an original Sillence classification [3]. Recently, a new OI classification was published that included 16 different genes responsible for this disease [4]. That implies the personalized medical treatment approach. In the same course, if the OI patients are treated with early and lasting bisphosphonate therapy and nonelongating fixation implants, they may develop unique long-bone deformities and the external/internal bone morphology leading to personalize surgical treatment approach.

Materials and methods

To illustrate personalized approach in the treatment of OI patients, we present the case of an 11-year-old girl with OI type III who had multiple surgeries with nonelongating implants during her childhood. At admission, she had a severe angular deformity of both the femur and the lower legs. At presentation to our hospital, she was unable to walk even with assistance, and used a wheelchair. According to Holden classification (Functional Ambulation Classification – FAC), she was FAC level 1 – Nonfunctional Ambulatory [5]. 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 a surgery on both lower legs. We first extracted the titanium elastic stable intramedullary nail – ESIN (Nancy) from the left femur and then made a double osteotomy of both femurs with fixation with Fassier–Duval telescopic intramedullary nails. Five months after the first hospitalization, the patient was once again admitted to our hospital in order to have a surgery on both lower legs. We performed 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. Figures 1 and 2 show both the femur and lower legs preoperatively and ~ 2 months after the second surgery. Radiographs had a good mechanical axis and correct position of distal threading. Ten weeks after the second surgery, she started to walk with a walker on
level surfaces, and 5 months after the second surgery, she was able to walk with the crutches. Finally, 7 months after surgery, she walks independently or sometimes with crutches, and she is able to climb the stairs (FAC level 6). However, a 2-year follow-up revealed no changes in the patient’s status.

Discussion
There are a lot of clinical and genetic classifications with many types and subtypes of OI. Because of this reason, it is not possible to make an algorithm of treatment and universal approach, which will be useful and successful for every patient. In case of OI, 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 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. Actually, two different mutations with clinical relevance in the collagen type I alpha1 chain (COL1A1) gene were detected, and mutations in the collagen type I alpha2 chain (COL1A2) gene were excluded with 98% probability. We believe that the molecular genetic analysis including determination of mutation as well as the type of OI may determine the type of surgery. To the best of our knowledge, there is no algorithm of OI treatment, and it is difficult to believe that we will be able to create a universal approach and algorithm. However, maybe tools such as Artificial Neural Networks used for machine learning will help to make the precise algorithm in the years to come. However, molecular genetic analysis helps to understand more details of 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 [6]. Nevertheless, mutations positioned at the C-terminal end of the alpha2 chain are

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).
not only related to limb anomalies but also to intracranial hemorrhage [7].

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 is presented here is an example of a severe case of OI. She has OI type III, angular deformities of her thighs and lower legs that are 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, remodeling of her bones was slowed down, and the intramedullary canal was filled with sclerotic bone. Because of the sclerotic intramedullary canal, it could be very difficult to pass the narrow or obliterated sites of the diaphyseal bone. This can extend the time of the operation and also lead to some complication like perforation of the bone cortex, malposition of the distal threading and increasing blood loss. Preoperative radiographs clearly 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 requires careful preoperative planning of the osteotomy level and the size/angle of the excised bone wedge. All of 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, the last but not the least, correction of the deformity. In this paper, we have presented our
diagnostic/treatment concept, which we arrived at on the basis of our experience with 12 operated patients and 31 operated segments (long bones). 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 our hospital.

**Conclusion**

According to the literature, more than 800 different mutations have been described in the COL1A1 and COL1A2 genes, so far [8]. To target a specific mutation (allele-specific silencing of COL1A1) and to reduce the amount of mutant collagen protein (converting a severe phenotype to mild OI), to introduce a procollagen cDNA expression construct to replace the lost activity of suppressed transcript and to create allele-specific suppression of a mutant collagen gene, either at the genetic or RNA level, are the ultimate challenges [9,10]. However, the final goal of the personalized medicine treatment concept in patients with OI will be silencing or replacement of the allele containing the causative variant by modifying mesenchymal stem cells in vitro and then either prenatally or postnatally returning those cells back to the patient. Until then, we believe that a personalized approach is the best option for those children.

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**Conflicts of interest**

There are no conflicts of interest.

**References**