Multiple epiphyseal dysplasia with contribution of two cases with a mutation in the COMP gene

Milka Dikova[1,2], Mihaela Blazheva[1](✉), Oleg Mladenov[1,2], Darina Kachakova [3],

[1]Medical University –Sofia, Sofia, Bulgaria
[2]University Orthopedics Hospital "Prof. B. Boichev" –Sofia, Bulgaria
[3]Center for Molecular Medicine, Department of Medical Chemistry and Biochemistry, Medical Faculty, Medical University – Sofia.

mihaela.blajeva@gmail.com

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Abstract- Multiple epiphyseal dysplasia (MED) is a heterogeneous group of inherited skeletal disorders characterized by abnormal development of the epiphyses. Patients with MED typically present with joint pain, stiffness, and a waddling gait, which often become symptomatic in childhood or early adolescence. Radiographic features include irregular, flattened epiphyses and delayed ossification. The condition can lead to early onset of osteoarthritis. Mutations in six different genes can cause the disease; these may be inherited in an autosomal dominant or autosomal recessive manner, or occur as a "de novo" mutation. Molecular diagnostics are important for accurate prognosis and genetic counseling.

Key words: - multiple epiphyseal dysplasia, COMP, delayed ossification, genetic mutations, joint pain

1. Introduction

Multiple epiphyseal dysplasia (MED) is a relatively rare skeletal dysplasia from the group of osteochondrodysplasias. It is caused by mutations in six genes - COMP, DTDST, MATN3, COL9A1, COL9A2, COL9A3, which encode the synthesis of extracellular components of the cartilage matrix (type 9 collagen chains and some specific proteins). The disease is inherited autosomal-dominant and autosomal-recessive, affecting the ossification nuclei of long bones. Dystrophic changes are observed in the structural elements of the epiphyses (bone beds and the tissue between them) with dilated blood vessels and growth of connective tissue. The growth zone is thinner, dystrophic changes are established in the articular cartilage.

MED proceeds with clinical variability, altering the axes of the long bones of the lower limbs and leading to early onset osteoarthritis (14-15 years of age), mainly of the hip and knee joints, with patients remaining mildly to moderately short in stature. The development of the disease also affects the muscles, with the development of atrophy, accompanied by muscle fatigue and pain. No visceral manifestations are observed.

A timely clinical diagnosis is extremely important for monitoring the musculoskeletal manifestations, their progress and conducting timely surgical treatment to prevent

complications. Balev and colleagues examined the radiological changes in 9 patients between 6 and 64 years of age, 5 from one family in 2002[1]. Confirmation through genetic diagnostics has become possible in recent years in Bulgaria. We present two children with MED and established mutations in the COMP gene.

2. Clinical case 1

A 13-year-old girl, born from a second normal pregnancy, by caesarean section, weighing 3760 grams, with frequent infections until the age of 9, with early adenotomy and placement of ventilation tubes in the ears. At the age of 11, a progressive distortion of the left knee began with pain, fatigue to the point of being unable to walk. Parents reported a family burden of joint disease: mother with knee osteoarthritis, maternal grandmother and maternal grandfather with hip and knee osteoarthritis from a young age.

Upon admission to the Children's Orthopedics Clinic of the University Hospital "Prof. Boycho Boychev", the child is in good general condition, with height - 147 cm, SDS height - /-1.97/ and weight - 40 kg., with generalized muscular hypotonia. The respiratory and cardiovascular systems are without deviations, the abdomen is soft, without organomegaly, the neurological status is normal. The child has an independent gait with a left-sided limp. There is a flexion contracture in the right knee joint S15-130 and a pronounced valgus deformity of the left knee joint, with limited movements in the hip joints, left R25-0-30 and right R25-0-20, respectively.

Radiographs of the lower extremities showed a left knee valgus of 37 degrees with roughness and loosening of the distal femoral and proximal tibial epiphyses and Perthes-like changes in the proximal femoral epiphyses. (Fig. 1)

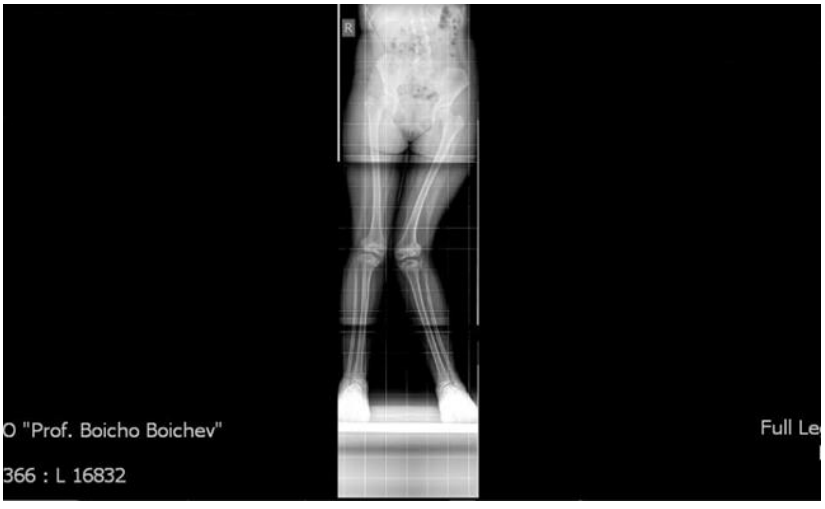

Fig.1 FLFS with valgus in the left knee joint of 37 degrees and of 13 degrees in the right

Molecular genetic analysis identified pathogenic variants in the heterozygous state of c1417_1419dupGAC (p.Asp473dup), rs193922900 in exon 13 of the COMP gene (NM_000095.3; NP_000086.2), encoding a pentameric extracellular matrix protein that catalyses collagen formation and initiates fibril formation. (OMIM*600310).

Under spinal anaesthesia, a temporary medial epiphysiodesis of the left distal femur and left proximal tibia was performed with placement of a Hinge plate and screws. (Fig. 2)

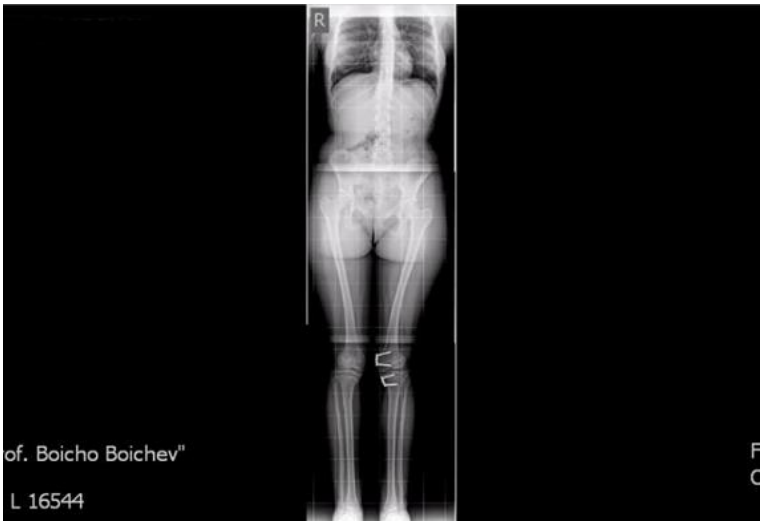

Fig. 2 FLFS postoperatively, placed two Hinge plates in left distal femur and left proximal tibia medially

3. Clinical case 2

It concerns a 7-year-old boy, from the first in vitro twin pregnancy, in the 3rd trimester, the development of the other embryo stopped. The birth was in 38 gestational week, by caesarean section, weighing 2560 grams, 45 cm, with proper neuro-psychological and physical development. It started walking at 1 year, 1 month, and at the age of 3-4, complaints of pain in the legs appeared, which at 5 years, 6 months. are localized in the knees. At this age, a diagnosis of Juvenile Idiopathic Arthritis was made with a hospital stay in the Children's Rheumatology Clinic. Around the age of six, a distortion

of the right knee joint in a valgus deformity was noticed, which was the reason for hospitalization in the Children's Orthopedic Clinic of USBALO Prof. Boycho Boychev.

Upon admission, the child was 118 cm tall, SDS height - (-1.4), weight - 22 kg, eumorphic face, head with a narrower lateral diameter, circumference 52 cm. Respiratory and cardiovascular systems were without deviations, the abdomen is soft, without organomegaly. There are flexion contractures in the elbow and knee joints with valgus of the right knee joint of 15 degrees, the neurological status is without deviations. The tests of calcium, phosphorus, parathormone are within reference limits, the mucopolysaccharides in the urine have normal values, and a latent deficiency of vitamin D is established.

X-rays of lower limbs and hands show a delay in bone age of about 1.5 - 2 years. (Fig 3.) A windswept right knee joint valgus was observed, with conical epiphyses of the phalanges of the hands, small proximal epiphyses of the femurs, and loose metaphyseal plates of most large joints. (Fig.4) There are clinical and radiological data for a dysplastic disease with the greatest probability of MED, which there is the greatest coincidence of signs, onset and course for.

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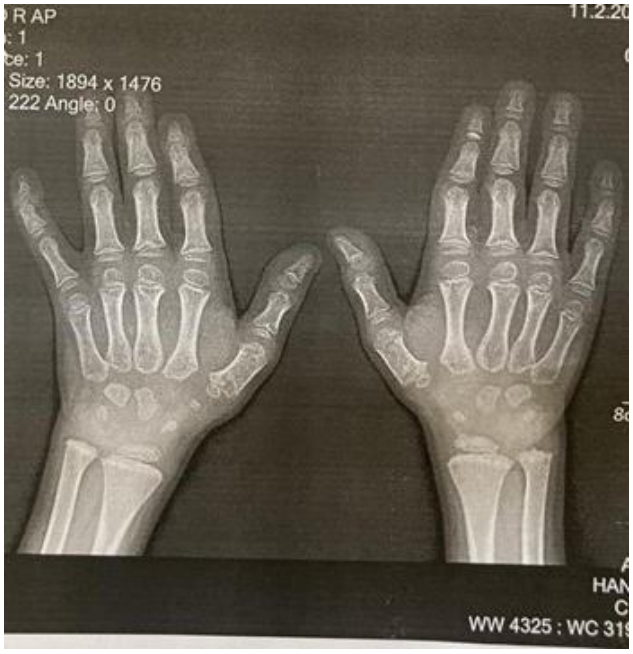

Fig. 3 X-ray of hands, with delayed bone age

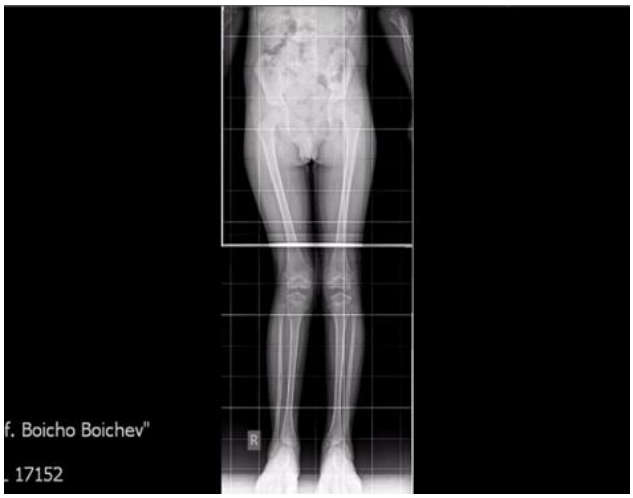

Fig. 4 FLFS preoperatively, with valgus in the right knee joint

The result of the molecular genetic analysis showed a pathogenic variant in a heterozygous state of p.1754>G(p.Thr585Arg), rs312262900 in exon 16, of the COMP gene (NM_000095.3, NP_000086.2), encoding a pentameric extracellular matrix protein catalysing the formation of collagens and initiating fibril formation (OMIM*600310).

Under spinal anaesthesia, a medial, temporary epiphysiodesis of the right distal femur is performed with placement of a Hinge plate and two screws. (Fig. 5)

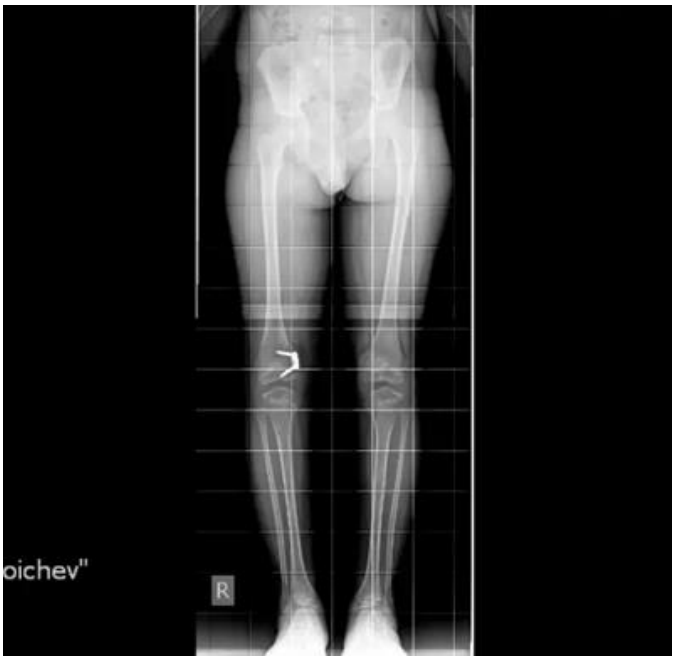

Fig. 5 FLFS postoperatively Placed Hinge plate in right femur medially

4. Discussion

Multiple epiphyseal dysplasia (MED) is a clinically and genetically heterogeneous disease characterized by mild stunting, changes in the axes of the long bones of the lower limbs, joint pain, and early onset of osteoarthritis and muscle hypotonia. MED is caused by mutations in genes encoding important cartilage extracellular matrix proteins, enzymes and transport proteins. Mutations were found in six genes - COMP, DTDST, MATN3, COL9A1, COL9A2, COL9A3, which can be inherited both autosomal dominantly and autosomal recessively[4]. The end result is disorganized endochondral ossification of the epiphyses of long bones. The articular cartilage at these sites is initially normal but rapidly degenerates due to the lack of underlying bony support.

Our clinical cases present the most common form of MED – COMP-MED (EDM1). It is inherited dominantly, but can also be observed as a "de novo" mutation. In the first case, there is a familial relationship, while in the second case, such is not established. Newborns are clinically healthy and of normal height. In the first months, no deviations from motor development are observed, but walking may be delayed due to hypotonia and hypermobility in the joints. This is one of the first symptoms of the disease. Growth retardation is noticed after two years of age affecting the limbs. Other symptoms are early fatigue during prolonged walking or playing, limited range of motion, limping

and pain in knees, hips and shoulders, brachydactyly. In the two presented children, we notice fatigue and pain in the lower limbs when exercising, with low growth.

With COMP-MED, a delay in the appearance of the carpal bones is observed. During ossification, the contour is irregular, sometimes jagged. The phalanges may be slightly shorter, and their epiphyses may be rounded or conical. Maturation delay affects the carpal bones more than the phalangeal epiphyses. The spine is not affected in childhood. The proximal femurs show a significant delay in maturation and the femoral head remains small and round for much longer than usual. In the knee joint, the distal femoral and proximal tibial epiphyses are too small for chronological age during childhood. The peripheral portion of the metaphysis is also undermineralized, resulting in an "ice cream cone" appearance. The radiographs of the presented patients show a delay in the bone age in the second patient, with conical epiphyses of the phalanges of the hands. The clinical cases have changes in the proximal and distal epiphyses of long bones of the lower limbs and fissured metaphyseal plates of most major joints.

Genetic diagnosis was performed in both patients with skeletal dysplasia, which confirmed the clinical diagnosis of MED. A pathogenic COMP mutation is found in 50% of patients with autosomal dominant MED[5], such was also found in our two children.

In the patient with family history of skeletal dysplasia (a pedigree shown in figure 6) c.1417_1419dupGAC (p.Asp473dup) variant in COMP was found. This variant is duplication of three nucleotides and leads to duplication of aspartate amino acid at 473rd protein position in type III repeat region of the protein. It is reported in ClinVar (Variation ID:9193) as pathogenic/likely pathogenic and was found in patients with multiple epiphyseal dysplasia. At the same position there are other known pathogenic variants like c.1405GAC[4] (p.Asp473del) and c.1418A>G (p.Asp473Gly) also detected in patient with multiple epiphyseal dysplasia. In population data bases like GnomAD c.1417_1419dupGAC (p.Asp473dup) is not found. According to ACMG criteria this variant was classified as likely pathogenic as it meets criteria PM1, PM2, PP4, PP5.

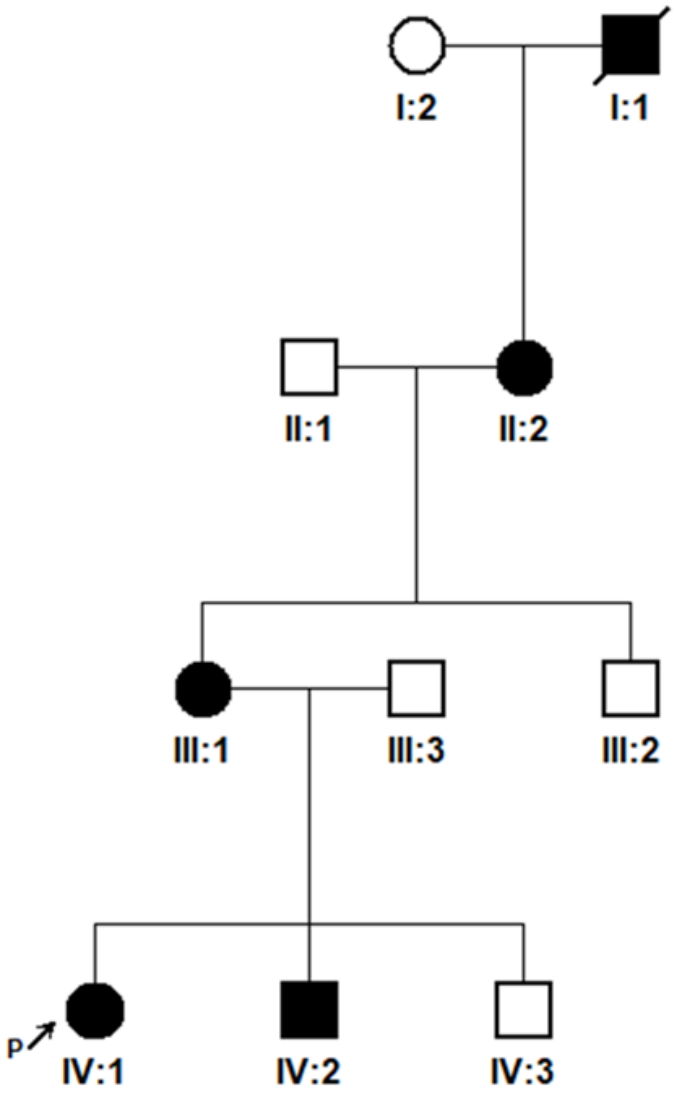

Figure 6. Pedigree of the patient with c.1417_1419dupGAC (p.Asp473dup) variant in COMP. The patient (proband) is shown with an arrow. Affected members of the family are colored black.

Accordingly in our second patient with no family history of skeletal diseases we found the variant c.1754C>G (p.Thr585Arg) in *COMP*. This is a missense variant which causes amino acid substitution in C terminal TSP protein domain binding three calcium ions. In ClinVar it is reported as pathogenic, and it was also detected in patients

with multiple epiphyseal dysplasia and it is not found in the population database GnomAD. It is classified as pathogenic according to ACMG classification criteria. This variant was not found in the patient's parents, so it is de novo (*figure 7*).

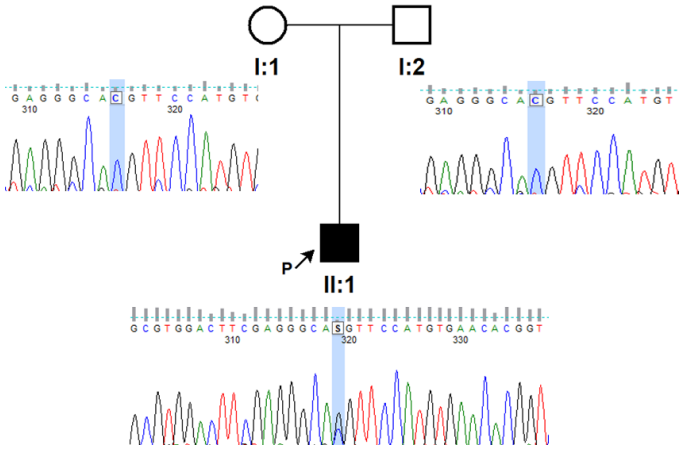

Figure 7. Variant c.1754C>G (p.Thr585Arg) in COMP identified in the analysed patient. The variant found from WES analysis was confirmed by direct sequencing. Electropherograms for the patient and his parents showing the COMP variant was de novo.

The differential diagnosis of MED (multiple epiphyseal dysplasia) includes Legg-Calvé-Perthes disease, spondyloepiphyseal dysplasia (SED), congenital hypothyroidism, mucopolysaccharidoses, and pseudo achondroplasia. The progression of Perthes disease (fragmentation followed by recovery) is significantly different, usually unilateral, and involves only the femoral heads while other epiphyses remain normal. SED is caused by a mutation in the COL2A gene and presents with joint manifestations similar to MED. SED also shows abnormalities in the vertebral bodies with the development of scoliosis, whereas MED usually does not involve the spine; if present, spinal changes appear later in life and do not progress. Mucopolysaccharidoses types IV and VI can be differentiated with additional tests, the first of which is the detection of mucopolysaccharides in the urine. Congenital hypothyroidism is a condition screened for neonatally in Bulgaria. Pseudo achondroplasia is diagnosed in patients with more severe growth retardation, marked joint laxity, and radiographic changes in the spine, metaphysis, and epiphyses of the long bones.

The treatment of children with MED aims to delay the onset of early osteoarthritis, improve the function of affected joints, and educate patients and their families about the genetic basis of the disease. Non-surgical treatment includes anti-inflammatory medications for pain control, physical therapy, and activity modification and forms the

foundation of initial medical care. Weight management and avoiding high-impact activities are essential to minimize stress on affected joints. Our second patient was initially treated with anti-inflammatory medications for a different diagnosis.

In cases of significant symptoms and/or limb deformities, surgical intervention may be indicated to relieve pain, improve movement, and correct the mechanical axis, although MED rarely requires surgical treatment in early childhood. Aligning the longitudinal axis of the long bones of the lower limbs is crucial because it ensures even loading across the entire growth plate area, which supports balanced bone growth and prevents the recurrence or worsening of existing deviations. Proper loading of the bone trabeculae activates the uniform emergence of physiological piezoelectric potentials in hydroxyapatite crystals, ensuring proper bone growth with the available bone potential without depolarization, which exacerbates the bone axis deformity.

Numerous surgical options have been described for correcting the longitudinal axes of long bones: temporary and permanent hemiepiphysiodesis, various corrective (varus, valgus, derotational) osteotomies, fixed with appropriate osteosynthesis devices. For combined corrections, including bone lengthening, external fixators are used for gradual correction of deformities and corresponding elongation.

The severity of hip joint deformities varies significantly with or without acetabular changes in MED. Osteotomy should be individually planned and should aim to correct varus or valgus deformities and maintain a more spherical and centered femoral head. Trochanteric descent plasty, varus or valgus intertrochanteric osteotomies, and various acetabular or pelvic osteotomies can be used for this purpose. The extent of involvement of the proximal femoral epiphyses in our patients does not require surgical treatment.

Distal femoral and proximal tibial osteotomies can be performed to correct varus or valgus deformities in the knees. These procedures are recommended for patients with completed bone growth who have severe deformity or for skeletally immature patients where growth modulation has been unsuccessful or is contraindicated. The clinical cases we present are not indicated for such surgical treatment.

The "Growth Guidance" method, which uses the unique growth potential of the pediatric bone, has gained popularity over the past decade. With this method, blocking the growth zone of a bone on one side while allowing unhindered growth on the other side compensates for existing angular deformity. The first results using a plate with two screws were reported by Goldman and Green in 2010, and the method has been used from 2 years and 6 months of age[2].The method was first applied in Bulgaria by our team in 2012 for the treatment of hypophosphatemic rickets[3].The surgical treatment chosen for the cases we present is temporary epiphysiodesis.

5. Conclusion

Multiple epiphyseal dysplasia is a clinical, radiological, and genetic diagnosis. Establishing it is crucial for effective treatment, improving quality of life, and preventing long-term complications. The results of molecular genetic analysis are important for

conducting medical-genetic counseling for the family and for future family planning of the affected children.

6. References

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7. Authors

Milka Dikova, MD is Assosiate professor at Medical University –Sofia, Department of Pediatrics. She works in the Orthopedic Hospital „Prof. Boycho Boychev “. Specialist in pediatric diseases and perioperative medicine. Head of the Children’s Sector in the Intensive Care Unit.

Mihaela Blazheva is a final year medical student at Medical University-Sofia.

Oleg Mladenov is a member of the Bulgarian Orthopedic and Traumatology Association (BOTA). He works as orthopedic surgeon at Orthopedic „Prof. Boycho Boychev“.

Darina Kachakova-Yordanova, PhD is a member of the Center for Molecular Medicine, Department of Medical Chemistry and Biochemistry, Medical Faculty, Medical University – Sofia. She holds a Doctor of Science degree with a specialization in Molecular Genetics.