DOI: https://doi.org/10.17650/2222-8721-2022-12-2-37-46

Differential diagnosis of myopathy and multiple epiphysal dysplasia caused by mutations in the *COMP* gene in children

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Background. Multiple epiphysal dysplasia (MED) type 1 (OMIM: 132400) is one of 7 genetic variants of this group of skeletal dysplasias described to date. The disease is caused by mutations in the *COMP* gene located on chromosome 19p13.1. The presence of muscle hypotonia and ligamentous laxity, as well as a moderate increase in the level of creatinephosphokinase activity, can lead to misdiagnosis of myopathy.

Aim. To analyze the clinical and genetic characteristics of MED type 1 caused by mutations in the *COMP* gene in a series of Russian patients. Differential diagnosis was focused on the distinctive features of the disorder and hereditary myopathies.

Materials and methods. We observed 8 patients from 7 families aged 7 to 15 years with MED type 1 caused by heterozygous mutations in the *COMP* gene. To confirm the diagnosis, the following methods were used: genealogical analysis, clinical examination, neurological examination with psycho-emotional testing, radiography and targeted sequencing of a panel consisting of 166 genes responsible for the development of inherited skeletal pathology.

Results. Case history, clinical, radiological and genetic characteristics of 8 patients with MED type 1 caused by mutations in the *COMP* gene were analyzed. The first clinical manifestations of the disease were recorded from the age of 2–3 years and were characterized by gait disturbances, muscle weakness, difficulties with climbing stairs, frequent falls when walking, the inability to get up from the floor and from a squatting position and hypermobility of the joints. Electroneuromyographic study did not reveal the signs of miopathy. In two patients, a moderate increase in the creatinekinase level of up to 250–360 U/l was found. All patients were surveyed by neurologists for several years with a clinical diagnosis of congenital myopathy. At the age of 5–6 years patients complained knee and ankle pain, which was assumed as rheumatic arthropathy. X-ray examination revealed typical signs of deficient ossification of the epiphyses. The next-generation sequencing analysis revealed seven single nucleotide variants in the *COMP* gene that lead to MED type 1. Three of the found variants here identified for the first time. As previously described, the majority of nucleotide variants (six out of seven) were localized in the 8–14 exons of the *COMP* gene and led to amino acid substitutions in calmodulin-like protein domain repeats, and only one substitution was localized in the C-terminal region of the protein molecule.

Conclusion. In most patients with MED caused by mutations in the *COMP* gene, the first symptoms of the disease are gait disturbance, muscle weakness, and Gowers' maneuvers. The presence of these symptoms, along with a moderate increase in the level of creatinephosphokinase activity, often precedes the onset of clinical manifestations of skeletal dysplasia, leading to a misdiagnosis with myopathies. Accession of expressive arthralgias to these symptoms was mistakenly identified as reactive arthritis. X-ray examination of patients' long bones helps to suspect the presence of MED. This X-ray imaging shows specific signs of epiphyses damage. A molecular-genetic analysis needs to be done to diagnose the genetic variant, caused by mutations in gene *COMP*.

Keywords: gene *COMP*, multiple epiphysal dysplasia, myopathy

For citation: Markova T.V., Kenis V.M., Nikitin S.S. et al. Differential diagnosis of myopathy and multiple epiphysal dysplasia caused by mutations in the *COMP* gene in children. Nervno-myshechnye bolezni = Neuromuscular Diseases 2022;12(2):37–46. (In Russ.).

DOI: https://doi.org/10.17650/2222-8721-2022-12-2-37-46

Background

Multiple epiphyseal dysplasia (MED) is a group of genotypically and phenotypically heterogeneous skeletal dysplasias, pathogenesis of which is associated with impaired ossification of the epiphyses of long bones and vertebral bodies [1]. The disease was first described by Thomas Fairbank in 1946 [2]. About half of MED cases are caused by *COMP* gene mutations responsible for MED type 1 with autosomal dominant inheritance [3]. Mutations in *COMP* gene in patients with MED were first identified by M.D. Briggs et al. in 1995 [4]. The *COMP* gene localizes on chromosome 19p13.1 and contains 19 exons. The protein product of this gene is a pentameric extracellular matrix glycoprotein expressed in cartilage, proliferative and hypertrophic chondrocytes in the growth plate of long bones, tendons, ligaments and skeletal muscles and involved in endochondral ossification, cartilage development and connection of muscles to their tendons [5, 6].

Unlike the most hereditary skeletal dysplasias, patients with this genetic variant of MED do not show significant growth retardation. Clinical signs manifest in early childhood and are characterized by motor impairment, waddling gait, easy fatigue when walking, difficulty climbing stairs and rising from horizontal position [7]. The presence of muscle hypotonia and ligamentous laxity, as well as mildly elevated levels of creatine kinase in the blood sample, often leads to misdiagnosis of myopathy for which patients are treated by neurologists [8]. After several years, above-mentioned symptoms are accompanied by pain in knee and ankle joints that is considered as manifestations of juvenile arthritis [3].

In most cases, patients do not undergo a specific X-ray examination, which obstructs the correct diagnosis and early management. Analysis of long bones radiographs is the most accurate way to assist differential diagnosis of hereditary myopathy, reactive arthritis and MED. Typical radiographic features of MED include delayed ossification of the femoral heads and carpal bones (delayed bone age), small and round shape of the epiphyses, the so-called "mini-epiphyses", which get "moon sickle appearance" and become fragmented and flattered with time [1, 3].

Therefore, the correct diagnosis and referral of patients to orthopedics occur only after several years after disease manifestation, which prevents timely treatment. It has been shown, that progressive degenerative changes in the hip and knee joints often lead to necessity of total joint replacement in adolescence [3].

The aim of the study is to analyze the clinical and genetic characteristics of MED type 1 caused by mutations in the *COMP* gene in a series of Russian patients and developing a differential diagnosis of the disorder and hereditary myopathies.

Materials and methods

We observed 8 patients from 7 families aged 7 to 15 years with MED type 1 caused by heterozygous mutations in the *COMP* gene. To confirm the diagnosis, the following methods were used: genealogical analysis, clinical examination, neurological examination with psycho-emotional testing, radiography and targeted sequencing of a panel consisting of 166 genes responsible for the development of inherited skeletal pathology. Isolation of genomic DNA was carried out from whole blood using the DNAEasy (QiaGen, Hilden, Germany) according to the manufacturer's standard protocol. The concentration of DNA and DNA libraries was measured on a qubit 2.0 instrument using reagents (qubit BR, qubit HS) from the manufacturer according to the standard protocol. For sample preparation, a technique based on multiplex polymerase chain reaction of target DNA regions was used. New generation sequencing was carried out on an Ion Torrent S5 sequencer with an average coverage of at least 80x; the number of targeted areas had coverage ≥90–94 %. To annotate the identified variants, nomenclature presented on site http://varnomen.hgvs.org/recommendations/DNA version 2.15.11 was used. Sequencing data were processed using a standard automated algorithm from Ion Torrent.

To assess the population frequencies of identified variants, samples of the "1000 Genome" projects, ESP6500, and The Genome Aggregation Database v2.1.1 were used. To assess clinical significance of the identified variants, OMIM database and the HGMD® Professional pathogenic variants database version 2021.3 were used. Assessment of the pathogenicity and causality of genetic variants was carried out in accordance with international recommendations for the interpretation of data obtained by massive parallel sequencing [9].

Validation of the identified variants in probands and genotyping of siblings and parents were carried out by automated Sanger sequencing according to the manufacturer's protocol on the ABIPrism 3500xl device (Applied Biosystems, Waltham). The primer sequences were selected according to the reference sequence of the *COMP* gene target regions (NM_000095).

Proband's parents gave informed consent to the clinical examination and the publication of their anonymized data.

Results

We analyzed anamnestic data, clinical, radiological and molecular-genetic features of 8 patients with MED, caused by variants in the *COMP* gene. In three families, the disease was inherited from either parent. The parents of patients with family history of disease complained of arthralgia in knee joints since childhood and were followed up by orthopedics with degenerative changes in hip and knee joints, resulting in bilateral coxarthrosis and gonarthrosis. In one case, joint replacement surgery of both hip joints was performed at the age of 25 and 26 years, respectively.

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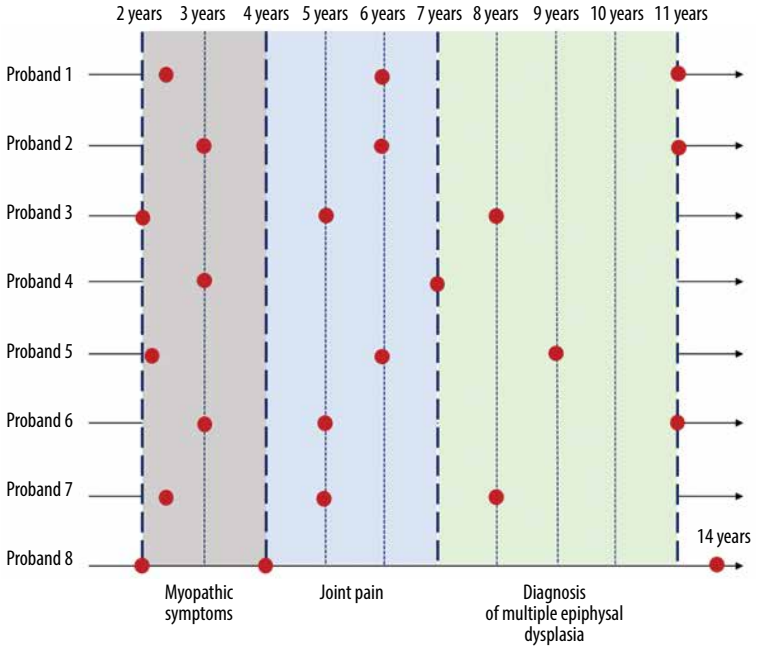

Fig. 1. *Age of symptoms onset and their characteristics in the patients of the surveyed sample*

of 166 genes responsible for the development of inherited skeletal pathology.

Analysis of disease course in patients showed that three of them had delayed motor milestones in the first year of life, however, the initial clinical features of the disease appeared at the age of 2–3 years and were characterized by changes in gait, fatigue, difficulty climbing stairs, frequent falls when walking, inability to stand up, joint laxity. On electroneuromyography there was no evidence of neuromuscular damage. Two patients presented with mildly elevated levels of creatine phosphokinase (CPK) of 250–360 U/l (normal range 190 U/l). All patients were followed up by neurologists with a diagnosis of congenital myopathy for several years. At the age of 5–6 years patients develop pain in the knee and ankle joints, which were interpreted as reactive, more often rheumatoid, arthritis. In half of the cases MED was not diagnosed until adolescence. The age of symptoms onset and their characteristics in the patients of the surveyed sample are shown in Fig. 1.

The clinical examination of patients aged 7 to 15 showed that their height matched the middle-lower bound of normal and ranged from –0.5 to –1.88 SD. Patients complained of gait disturbances, fatigue and pain in knee and ankle joints when walking. None of the patients showed significant shortening of the limbs, four probands had brachydactyly of hands, and two had stiffness in the elbow joints. Valgus knee was found in two probands, one of which required surgical correction: temporary hemiepiphysiodesis of the lower third of the femur on both sides at the age of 10 years. All patients present with ligamentous laxity of ankle joints, plano-valgus deformity of both feet, and a "waddling" gait.

A radiological data analysis of patients revealed typical signs of damage of long bones' epiphysis in the form of their deformities and reduction in size, height decrease, heterogeneous structure, sharp "mushroom-shaped" flattening of the femoral head, irregular contour and flattening of the femoral and tibia condyles. Spinal radiographic abnormalities were minimal and described as endplate irregularity.

Based on the anamnestic data, clinical examination and radiological features, the patients were expected to have one of the genetic variants of MED. As a result of the molecular genetic analysis, 7 variants in the *COMP* gene were found, three of which were identified for the first time. Spectrum of nucleotide variants in the *COMP* gene in patients with MED is presented in Table 1.

Six out of seven identified single nucleotide variants were missense, and in one case deletion of three nucleotides was found. Six single nucleotide variants were localized in exons 8–14 of *COMP* gene and led to amino acid substitutions in the calmodulin-like repeats of the protein. Only one substitution was localized in the C-terminal domain of the protein. Our data confirm the results of other studies [17, 18]. Localization of amino acid substitutions in *COMP* protein domains in Russian patients with mutations in the *COMP* gene is shown in Fig. 2.

To demonstrate the clinical features and disease course we report a case of thirteen years old boy, who was consulted about complaints of gait disturbances, fatigue when walking, joint pains, difficulties standing up from a squatting position. Both parents are healthy, the mother has a healthy 20-year-old daughter from her first marriage.

Table 1. *Spectrum of nucleotide variants in the COMP gene in patients with multiple epiphysal dysplasia*

Proband	Exon	Nucleotide variant	Amino acid substitution	Protein domain	Previously described
1	8	c.827C>G	p.Pro276Arg	$T3_1$	M. Czarny-Ratajczak et al. (2001) [10], T.L. Chen et al. (2008) [11]
2	9	c.886C>T	p.Pro296Ser	$T3_1$	–
3	11	c.1153G>A	p.Asp385Asn	$T3_4$	A. Mabuchi et al. (2003) [12], H.Y. Liu et al. (2017) [13]
4	11	c.1153_1155delGAC	p.Asp385del	$T3_4$	G.C. Jackson et al. (2012) [14]
5	13	c.1367A>C	p.Gln456Pro	$T3_6$	–
6	14	c.1501G>A	p.Gly501Ser	$T3_8$	–
7	14	c.1501G>A	p.Gly501Ser	$T3_8$	–
8	16	c.1754C>T	p.Thr585Met	CTD	M.D. Briggs et al. (1998) [15], T.L. Chen et al. (2008) [11], C.L. Hartley et al. (2013) [16]

Note. *Probands 6 and 7 are half-siblings with the same genotype.*

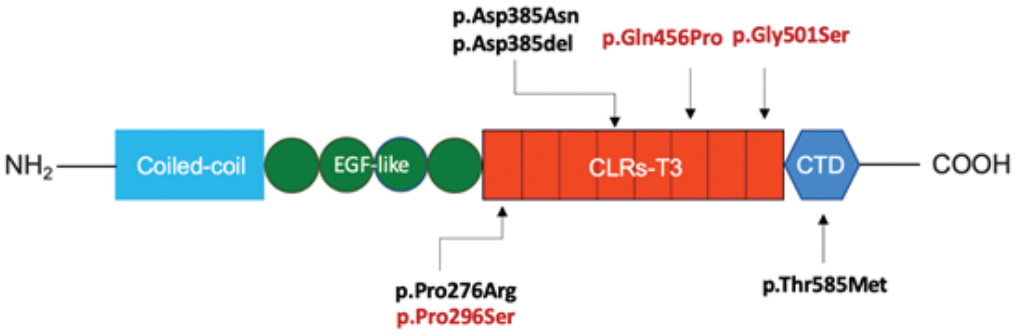

Fig. 2. *Localization of amino acid substitutions in COMP protein domains in Russian patients with mutations in the COMP gene. Newly identified variants are marked in red*

Clinical case

The boy was born from 4th pregnancy, 2nd premature birth at 40th week of pregnancy with birth weight 2450 g, height 46 cm, APGARS 7 and 8 at 1 and 5 min, respectively. On the first year of life, the patient got massage therapy, developmental milestones were delayed: sat since 8 months, walked since 1 year 2 months. On the second year of life, the parents noticed periodic "dragging" of the left foot, fatigue when walking (constantly asked to be held), inability to climb stairs, squat, get up from the floor on his own until the age of 5–6 years. The child was observed by neurologists with a diagnosis of "congenital myopathy". However, electroneuromyography did not show any signs of neuromuscular damage, laboratory investigations revealed mild elevation of CPK activity up to 230 U/l. At the age of 6 years, the pain in ankle joints and gait disturbance developed. Ligamentous laxity on the feet, fallen arch and valgus deformity of the feet, hypermobility in the wrist, elbow and knee joints were diagnosed by the orthopedist. At the age of 8 years, after an injury to the right outer ankle, foot radiographs in two projections were performed, where signs of chondropathy were found in the form of flattening and deformation of the heads of the metatarsal bones, blurred and uneven contours of the endplates of the tarsal bones of both feet, a consultation with a specialist in skeletal dysplasia was recommended. Only at the age of 11 the child underwent a complete radiological examination of the spine and joints of the lower extremities in H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery, based on which the presence of a hereditary MED was assumed.

On examination at the age of 13 years the height was 151cm (–0.89 SD), weight 41 kg (–0.41 SD), which corresponded to average harmonious physical development (Fig. 3a). Hypermobility in wrist, elbow, knee and ankle joints was noted (Fig. 3b). A slight asymmetry of the chest and a poor posture were revealed. Flatfoot valgus deformity of both feet was noted. The child had difficulties in squatting and getting up from squatting position, used Gowers' maneuver. In neurological status: No signs of paresis in the legs. No signs of muscle hypotrophy. Reflexes

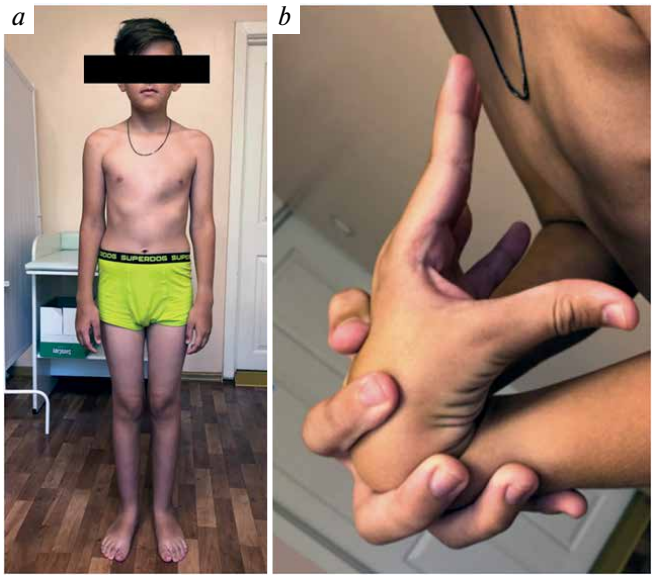

Fig. 3. *The appearance of the patient (a). Hypermobility of the joints of the upper limb (b)*

are 2/2 and symmetric, D = S. Muscle bulk and tone are normal. Sensory and coordination are intact.

The radiological examination revealed a moderate anterior wedging of the 7–9 thoracic vertebral bodies (Fig. 4a), the epiphyses of the femoral heads were reduced in size and had uneven contours (Fig. 4b). The radiographs also showed impaired ossification in the knee joints (Fig. 4c), valgus deformity of the ankle joints due to impaired ossification of the distal epiphysis of the tibia and talus block (Fig. 4d).

Based on the clinical and radiological features, the patient was expected to have MED type 1. The diagnosis was confirmed by molecular genetic analysis, in which a heterozygous single nucleotide variant in exon 9 of COMP gene (NM_000095): c.886C>T, p.Pro296Ser was identified. The identified variant was not registered in the GnomAD database, was not previously described in HGMD database, however, another variant, c.886C>A, p.Pro296Thr (CM1410526), was described in this codon. Algorithms for predicting pathogenicity define this variant as likely pathogenic (SIFT, Polyphen2_HDIV, Polyphen2_HVAR, MutationTaster, PROVEAN). The validation and segregation by the automated Sanger sequencing found detected variant in heterozygous state in the child and did not find it in the parents, which confirmed its de novo status.

Discussion

MED type 1 is hereditary skeletal dysplasia caused by mutations in the *COMP* gene located on chromosome 19p13.1. The protein product of this gene is a pentameric glycoprotein of extracellular matrix expressed in cartilage,

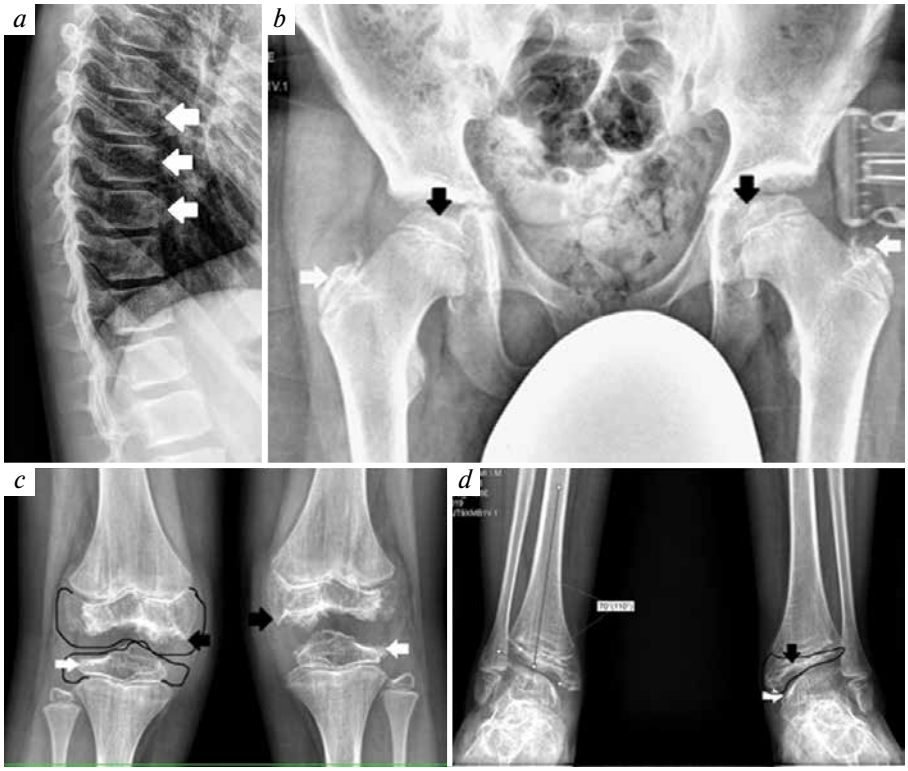

Fig. 4. *Patient radiographs: a – radiograph of the spine (lateral view): moderate wedging of the anterior aspects of the vertebral bodies of C7–C9 thoracic (white arrows) secondary to deficient ossification; b – radiograph of the hip joints: the epiphyses of the femoral heads are small and uneven (black arrows), deficient ossification of the greater trochanters on both sides (white arrows); c – radiograph of the knee joints: deficient ossification, irregularity, extra ossification centers of the femoral (black) and tibial (white calibers) epiphyses; the estimated cartilaginous epiphyses are contoured as black lines; d – radiograph of the ankle joints in direct projection: valgus deviation of the distal lateral tibial angle (70°, normal range – 86–92°), deficient ossification, irregularity, extra ossification centers of the distal tibial epiphysis (black arrow) and a dome of the talus (white arrow), the estimated cartilaginous epiphysis is contoured as black line*

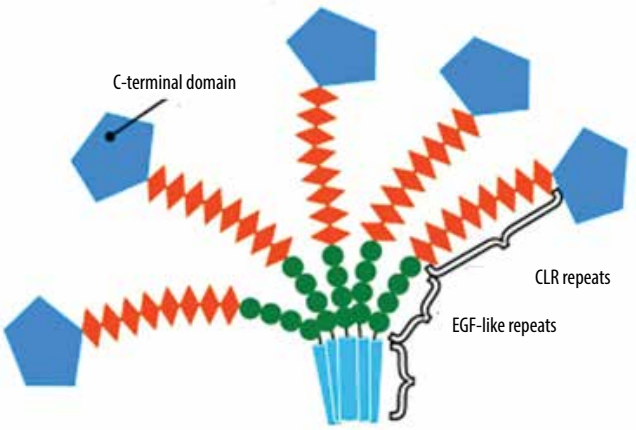

Fig. 5. *Domain structure of the COMP protein*

ligaments and muscles. COMP is considered to be a catalyst in collagen fibrillogenesis [19]. Through interactions with other proteins, such as type II and IX collagen, matrilin-3, aggrecan and fibronectin, it forms a macromolecular network and, in particular, connects the muscle to its tendon [20].

The protein is shown to consist of N-terminal oligomerization domain (coiled-coil), four epidermal growth factor-like repeats (EGF-like/T2), eight type 3 calmodulin-like repeats (CLR/T3 repeats), and a globular C-terminal domain. (CTD) [21]. The protein is a homopentamer in which the N-terminal domain mediates pentamerization, resulting in a bouquet-like organization of the five monomers (Fig. 5). The T2, T3 repeats, and CTD domains bind calcium ions, which is critical for proper folding and secretion of the COMP protein. In addition, the C-terminal globular domain is required for interaction with fibrillar and non-fibrillar collagens and other extracellular matrix proteins and the formation of calcium-binding site [11].

As in most cases of MED type 1 reported in the literature, in our sample of patients the majority of nucleotide variants (6 out of 7) were missense substitutions localized in T3 repeats of the calmodulin protein domain, which are encoded by exons 8–14 of the *COMP* gene. In only one patient, the missense variant p.Thr585Met previously described as pathogenic was identified in the C-terminal protein domain [11, 15, 16]. Our results confirm the data of other studies that showed that 90 % of all mutations causing MED type 1 is localized in the type III repeat domain (T3-COMP) which consists of amino acid residues arranged into eight consecutive T3 repeats. Mutations in the C-terminal globular domain encoded by exons 15–19 are found in no more than 10 % of patients and cluster in two distinct regions of this domain: at 583, 585, 587 and 718, 719 amino acid residues [17, 18].

Analysis of anamnestic data and clinical presentation in patients with MED type 1 observed by us and reported in literature revealed that the first signs of the disease manifesting in early childhood include changes in gait, increased muscle fatigue, difficulty climbing stairs and getting up from a squatting position, that leads to misdiagnosis of congenital myopathy. In addition, this diagnosis is suspected because of the presence of delayed motor milestones, moderate muscle hypotony, mild elevation of CPK levels and signs of the primary muscular damage recorded during the EMG study, which are found in some patients with MED type 1. The presence of these symptoms leads to misdiagnosis of myopathy, observation and treatment of patients by a neurologist. It must be noted that these patients do not have depressed deep tendon reflexes, typical in congenital myopathies. It has been shown that significant symptoms of myopathy are typical for mutations that change amino acid sequence in C-terminal domain. E. Jakkula et al. reported a family with five affected members in three generations who had p.Arg718Trp mutation in *COMP* gene, two of them presented with muscular weakness and moderately raised creatine kinase from 440 up to 1647 U/l, because of which they were evaluated by a neurologist with diagnosis of myopathy [22]. Elevated CPK levels were also noted in two other members of this family with clinical and radiological signs of MED in the absence of myopathic symptoms. G.C. Jacobse et al. in 2012 reported a 7-year-old boy with p.Thr585Lys mutation, who was observed by a neurologist from the age of 3 with a diagnosis of congenital myopathy. The diagnosis of MED type I was suspected only after radiological examination and molecular-genetic testing [14]. To explain the presence of myopathic symptoms in patients with MED I, K.A. Pirog et al. analyzed phenotypic and morphological changes in knockout mice resulting from p.Thr585Met mutation in the *COMP* gene. Morphology of skeletal muscles, achilles tendon and intervertebral discs was examined by the authors. It was shown that the mild signs of myopathy seen in them were due to abnormal structure of the perimysium, as well as myotendinous junction and an increased number of fibers with central nuclei [6]. Thus, it was concluded that the symptoms of myopathy are the result of tendopathies, and the hypermobility of the joints is due to structural disorders in the myotendinous junction. However, morphological studies in muscle biopsies of patients with MED type 1, conducted by J. Kennedy et al. in 2005 showed that in some cases they also have atrophy and a change in the diameter of muscle fibers [18].

Conclusion

Studying of anamnestic data and clinical and radiological features in Russian patients with MED type 1 caused by mutations in *COMP* gene and analysis of previously reported patients revealed that the first signs of the disease in most patients manifesting at the age of 2–3 years include change in gait, increased muscle fatigue and Gower's maneuver. The presence of these symptoms, along with a mildly increased level of CPK, often precedes the onset of clinical manifestations of skeletal dysplasia, leading to misdiagnosis of a neuromuscular disease from the group of myopathies and long-lasting observation and treatment of patients by a neurologist, which delay an accurate diagnosis and proper treatment. A reliable radiological sign of MED type 1 in such patients is the presence of typical changes in the epiphyses

in the form of their deformities and reduction in size, and flattening with age, mainly seen in the articulating surfaces of the long bones of the thighs, knee joints, ankles, wrists and hands. In addition, specific signs of MED may include pain in the large joints of the lower extremities that occur without signs of reactive arthritis, which should also be taken into account when assist differential diagnosis of MED with myopathies and reactive arthritis.

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Authors' contributions
T.V. Markova, V.M. Kenis, S.S. Nikitin: study design development, literature review, writing and editing the article;
T.S. Nagornova: conducting laboratory molecular genetic diagnostics, analysis of results obtained, writing the article;
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Conflict of interest. The authors declare no conflict of interest.

Funding. State budget financing.

Compliance with patient rights and principles of bioethics. The study was conducted according to the guidelines of the Declaration of Helsinki, the study protocol was approved by the biomedical ethics committee of the Research Centre for Medical Genetics (protocol No. 2021-3 dated 12.03.2021). Legal representatives of patients signed written informed consent to molecular-genetic testing and publication of patients' anonymized data.

Article submitted: 02.04.2022. **Accepted for publication:** 29.04.2022.