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Case report

Mucopolysaccharidosis IVB and sensorineural deafness associated with the *CDH23* gene: A unique clinical case

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BACKROUND: Mucopolysaccharidoses are a group of lysosomal storage diseases belonging to orphan diseases. Certain types of mucopolysaccharides have a typical musculoskeletal findings and radiological changes. The mucopolysaccharidosis IVB is a rare type. Thus, >95% of cases of the mucopolysaccharidosis IV are subtype A.

CLINICAL CASE: Clinical and radiological changes and genetic examination were performed to a 9-year-old patient with sensorineural deafness who applied to a medical institution with complaints of right hip pain and limping.

DISCUSSION: Based on complaints and radiological changes of the hip joints, the patient was initially diagnosed with Legg–Calve–Perthes disease. The presence of a symmetrical bilateral process, pathognomonic changes in the acetabulum and femoral heads, and an atypical clinic of Legg–Calve–Perthes disease made us suspect mucopolysaccharidos. Enzymatic analysis revealed a significant decrease in the beta-D-galactosidase enzyme activity. In addition, two compound heterozygous variants in the *GLB1* gene were identified: the pathogenic variant c.808T>G, inherited from the father, and an insertion of a mobile genetic element, inherited from the mother. Only one variant in the *GLB1* gene was detected in the brother (born in 2009), and none of the above *GLB1* variants was detected in the older brother (born in 2003). Moreover, the proband (with clinical mucopolysaccharidos IVB) and his brother (born in 2009) (without mucopolysaccharidos IVB) inherited pathogenic *CDH23* variants (c.6992T>C and c.805C>T) from their mother and father, respectively, which is consistent with their having sensorineural hearing loss.

CONCLUSIONS: The uniqueness of this clinical case is the presence of the rare type of mucopolysaccharidos and the separate genetic cause of sensorineural hearing loss in a single patient. The diagnosis of mucopolysaccharidos IVB in the proband was confirmed by biochemical and molecular genetic tests, and the diagnosis of *CDH23*-associated sensorineural deafness in the proband and brother (born in 2009) was confirmed by molecular genetic testing.

Keywords: mucopolysaccharidosis IVB; orthopedics; dysostosis multiplex; hearing loss; Legg–Calve–Perthes disease; genetics.

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Клинический случай

Мукополисахаридоз IVB типа и нейросенсорная глухота, ассоциированная с геном *CDH23* (уникальный клинический случай)

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Обоснование. Мукополисахаридозы — группа лизосомных болезней накопления, относящихся к орфанным заболеваниям. Определенные типы мукополисахаридоза характеризуются типичной клинической картиной со стороны опорно-двигательного аппарата и изменениях на рентгенограммах. Мукополисахаридоз IVB типа — редкий подтип. Более 95 % выявляемых случаев мукополисахаридоза IV типа относится к подтипу A.

Клиническое наблюдение. Представлено описание клинико-рентгенологической картины и генетического исследования пациента 9 лет с нейросенсорной тугоухостью IV степени, обратившегося в лечебное учреждение с жалобами на боль в области правого тазобедренного сустава и хромоту.

Обсуждение. На основании жалоб и рентгенографии тазобедренных суставов пациенту первично был поставлен диагноз «болезнь Легга – Кальве – Пертеса» по месту жительства. С учетом симметричного двустороннего процесса, патогномоничных изменений вертлужной впадины и головок бедренных костей и нетипичной для болезни Легга – Кальве – Пертеса клинической картины у пациента был заподозрен мукополисахаридоз. При биохимической диагностике отмечено снижение активности бета-D-галактозидазы. Были также обнаружены компаунд-гетерозиготные варианты в гене бета-D-галактозидазы (*GLB1*): патогенный вариант c.808T>G, унаследованный от отца, и инсерция мобильного генетического элемента, унаследованная от матери. У брата 2009 года рождения выявлен только один вариант в гене *GLB1*, у старшего брата, 2003 года рождения, вышеуказанные варианты в гене *GLB1* отсутствовали. Пробанд с клинической картиной мукополисахаридоза IVB и его брат 2009 года рождения (без мукополисахаридоза IVB) унаследовали патогенные варианты c.6992T>C (p.Val2331Ala) и c.805C>T (p.Arg269Trp) в гене *CDH23* от матери и отца соответственно, что согласуется с существующей у них нейросенсорной тугоухостью IV степени.

Заключение. Уникальность данного клинического случая заключается в наличии у пациента редкого IVB типа мукополисахаридоза и не ассоциированной с ним нейросенсорной тугоухости IV степени. Диагноз мукополисахаридоза IVB типа у пробанда подтвержден биохимическими и молекулярно-генетическими методами, а диагноз «нейросенсорная глухота, ассоциированная с геном *CDH23*» у пробанда и брата 2009 года рождения — молекулярно-генетическим методом.

Ключевые слова: мукополисахаридоз IVB; ортопедия; множественный дизостоз; тугоухость; болезнь Легга – Кальве – Пертеса; генетика.

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ЭКО•ВЕКТОР

BACKGROUND

Mucopolysaccharidoses (MPS) are lysosomal storage diseases. Currently, seven types of MPS are known, which are caused by a deficiency of one of the eleven enzymes involved in the degradation of glycosaminoglycans.

- Type I is associated with alpha-L-iduronidase deficiency. It is subdivided into subtypes, namely, Hurler syndrome, Hurler–Scheie syndrome, and Scheie syndrome, which do not differ in such a pronounced clinical presentation [1].
- Type II (Hunter's syndrome) is caused by iduronate-2-sulfatase deficiency [2].
- Type III (Sanfilippo syndrome) is subdivided into subtypes: subtype A is caused by heparan-N-sulfatase deficiency, subtype B by alpha-N-acetylglucosaminidase deficiency, subtype C by acetyl-CoA-alpha-glucosaminide acetyltransferase deficiency, and subtype D by N-acetylglucosamine-6-sulfatase deficiency [3].
- Type IV (Morquio's syndrome) is subdivided into subtypes, where subtypes A and B are caused by N-acetylgalactosamine-6-sulfate-sulfatase deficiency and beta-galactosidase deficiency, respectively [4].
- Type VI (Maroteaux–Lamy syndrome) is associated with arylsulfatase B deficiency [5].
- Type VII (Sly's syndrome) develops with glucuronidase deficiency [1].
- Type IX occurs in hyaluronidase deficiency [6].

All MPS types are characterized by progressive changes in the osteoarticular system. The pathogenesis involves excessive accumulation of non-degraded glycosaminoglycans, which leads to the activation of pro-inflammatory cytokines, apoptosis of chondrocytes, and secondary hyperplasia of the synovial membrane of the joints [7–9]. These metabolic and inflammatory changes are manifested by a typical clinical and radiological presentation [10].

In MPS, X-ray images present multiple dysostoses characterized by an anomaly in the formation of the osteoarticular system over time. Macrocephaly, clavicular expansion, paddle-like costal deformity, hypoplasia of the odontoid process of the second cervical vertebra, atlanto-axial instability, vertebral ventral deformity with lumbar kyphosis, anisospondylia (uneven height of the vertebrae in the craniocaudal direction), epiphyseal flattening, metaphyseal zone expansion, acetabular dysplasia, insufficient ossification of the acetabular rim and femoral heads, a change in the proportions between the iliac wing width and body ("Mickey Mouse symptom"), and valgus deformity of the femoral necks are observed [11].

Orthopedic manifestations of MPS also include stenosis of the cervical and thoracolumbar spine, progressive scoliosis, multiple contractures, joint subluxations and dislocations, axial limb deformities, and carpal tunnel syndrome [12].

MPS type IVB is rare, and >95% of identified cases of MPS type IV are subtype A [13]. This is probably due to the more "mild" phenotypic forms of MPS type IV and the complexity of their clinical diagnostics [14].

This study presents the diagnostic results of a patient with a rare form of MPS type IVB and sensorineural deafness, which was not associated pathogenetically with storage disease.

CLINICAL CASE

Patient K., 9 years old.

Complaints. The parents with a child born in 2011 (9 years old at the time of the initial visit) presented to an orthopedist with complaints of pain in the right hip joint and gait disturbance, which appeared about 1 week before the visit. They denied having had injuries. Previously, the child was diagnosed with grade IV sensorineural hearing loss, and a cochlear implant was installed at the age of 8 months.

Anamnesis vitae. Obstetric and gynecological history was not complicated (delivery 3, timely). Psychomotor development corresponded to the patient's age. The patient has two older brothers, born in 2009 and 2003. The brother born in 2009 was diagnosed with grade IV sensorineural hearing loss, and a cochlear implant was installed in 2011. The middle brother had no history of complaints of gait disturbance and pain. *GJB2* mutations, which are the most common cause of hereditary hearing loss, were ruled out. The older brother (born in 2003) had hearing and musculoskeletal complaints and had no chronic diseases. The genealogy of the family is presented in Fig. 1 (the child born in 2011 is marked in the family tree as the proband).

During examination, the child was of normosthenic physique and had increased nutrition. A cochlear implant on the right was noteworthy. There was no prominent facial dysmorphism.

The gait was antalgic, with limping on the right lower limb, rotating it outwards. On examination, no signs of inflammatory changes were observed. Due to the pain syndrome, the range of motion in the right hip joint was limited, with flexion on the right and left of 100° and 120°, extension on the right and left of 0°–5° and 5°–10°, abduction on the right and left of 20° and 50°, adduction on the right and left of 15° and 25°, internal rotation on the right and left of 0° and 10°, and external rotation on the right and left of 40° and 50°, respectively. The intensity of the pain syndrome corresponded to 7 of 10 points according to the visual analog scale. A diagnosis of Legg–Calve–Perthes disease was presumably established.

From the anamnesis, gait disturbance appeared at the age of 6 years 10 months after an acute respiratory viral infection. There were no complaints of pain. By the time of treatment, the gait visually worsened, and pain was felt in the right hip joint, for which they turned to an orthopedist.

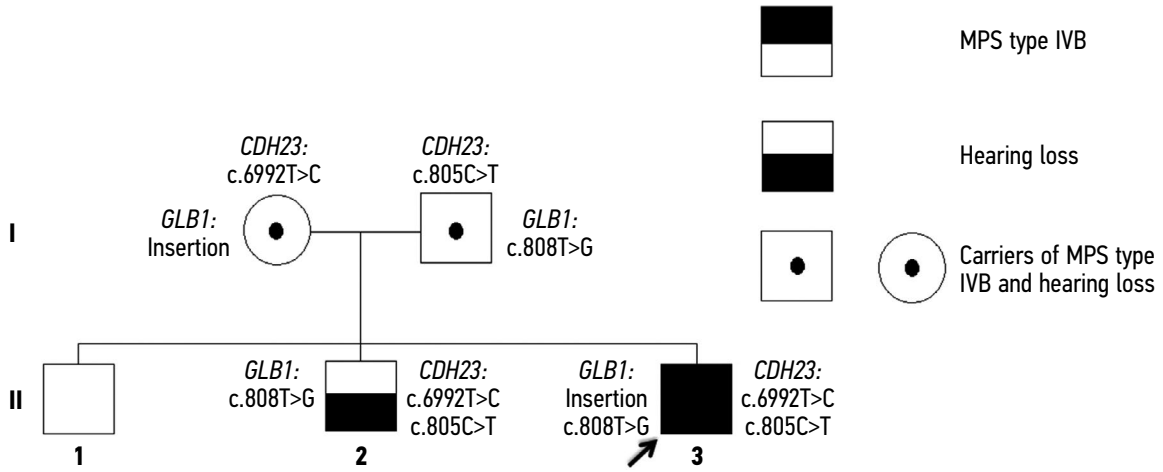

Fig. 1. Family tree of the proband. Generation I, white square and circle indicate the father and the mother, respectively; generation II, square 1 is the older brother born in 2003 without hearing loss, square 2 is the older brother born in 2009 with hearing loss, and square 3 with a black arrow is the examined patient with hearing loss (proband). MPS, mucopolysaccharidosis

Diagnosis. The plain radiograph of the pelvic bones presented bilateral acetabular dysplasia and deformed femoral heads. According to the study, bilateral Legg–Calve–Perthes disease was confirmed.

The child was consulted in absentia by the staff of the H.I. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery due to the symmetry of the lesion and clinical presentation atypical for Legg–Calve–Perthes disease. The diagnosis of MPS was suggested. Radiography of the spine in the lateral view and hands and knee joints in the frontal view was recommended.

Lateral radiograph of the thoracolumbar spine showed changes in the shape of the vertebral bodies according to the type of tongue-shaped deformity, anisospondylia, paddle-like costal deformity, as well as hypoplasia of the odontoid process of the second cervical vertebra, atlanto-axial instability, and deformity of the ventral parts of the cervical vertebrae (Fig. 2).

Radiographs of the hands and knee joints without significant changes (Fig. 3).

Moreover, the radiograph of the hip joints presents typical signs, as shown in Fig. 4.

In connection with the clinical and radiological presentation, enzymatic diagnostics (screening for lysosomal storage diseases) was performed at the Academician N.P. Bochkov Medical Genetic Research Center (Moscow). The results revealed a decrease in the activity of the enzyme beta-D-galactosidase, which is a biochemical marker of MPS type IVB.

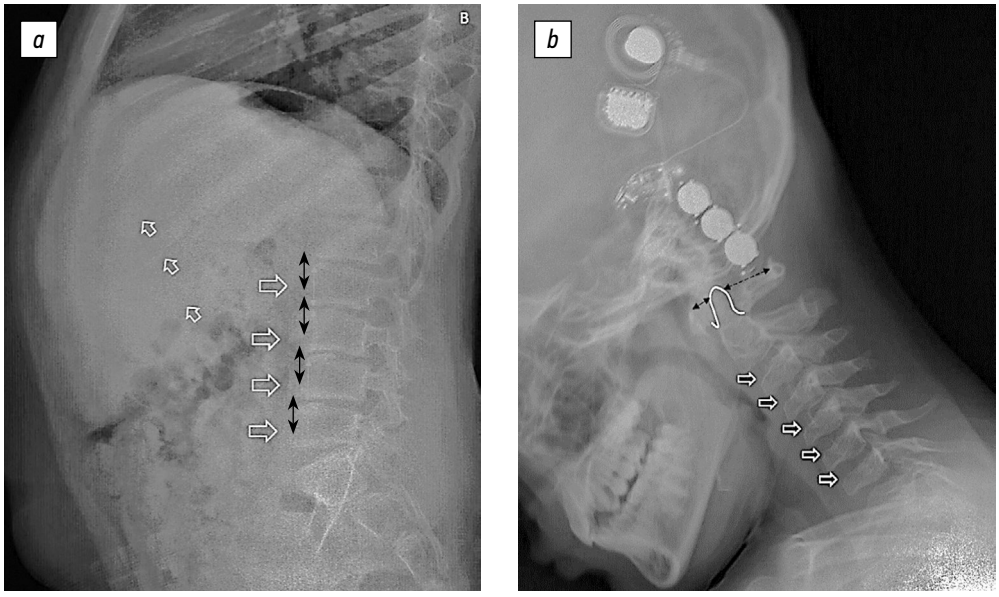

Fig. 2. Radiographs of the cervical and thoracic spine: *a,* white arrows indicate expansion of the intercostal spaces, paddle-like costal deformity, and deformity of the ventral vertebrae; blue-dotted line indicates anisospondylia with an uneven height of the vertebrae in the craniocaudal direction; *b,* white line indicates hypoplasia of the odontoid process of the second cervical vertebra, black arrows indicate signs of atlanto-axial instability, and white arrows indicate deformity of the ventral cervical vertebrae

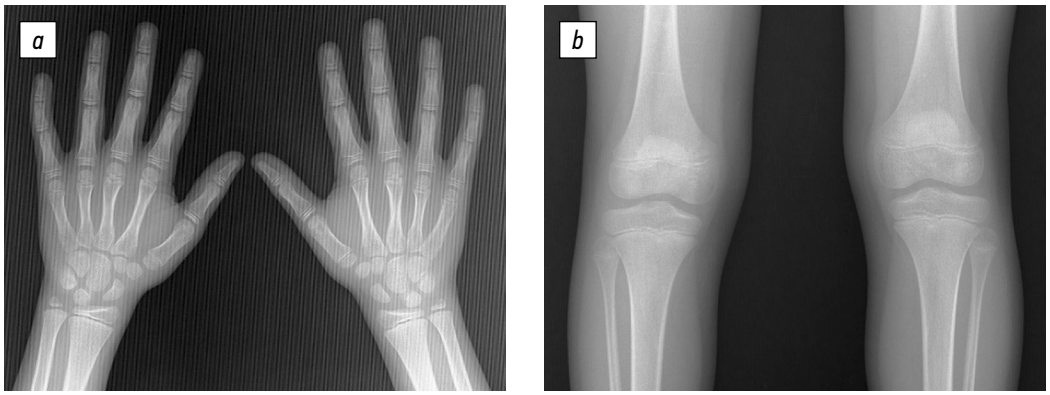

Fig. 3. X-ray images of the hands and knee joints in the frontal view

The results of repeated tests also revealed a decrease in the activity of beta-D-galactosidase. In the brothers of the proband, no data of a decrease in the activity of lysosomal enzymes were obtained (Table).

Owing to a decrease in beta-D-galactosidase activity, the proband underwent a complete analysis of *GLB1* (NM_000404.3) by direct automatic sequencing and exome sequencing. In both cases, in exon 8 of *GLB1*, only one pathogenic variant c.808T>G (p.Tyr270Asp) in the heterozygous state was detected, which, given the autosomal recessive type of MPS type IVB inheritance, is not sufficient to establish a molecular genetic diagnosis. Genome sequencing was performed to search for the pathogenic variant 2 in the gene, and the analysis of *GLB1* at the mRNA level was also conducted. According to the results of the genome sequencing in *GLB1*, in addition to the c.808T>G (p.Tyr270Asp) variant in the heterozygous state, data confirmed the insertion of a mobile genetic element from the class of retrotransposons. Subsequent functional analysis revealed that the insertion leads to impaired splicing of *GLB1* and is probably a pathogenic variant [15]. The identified variants in the proband and its relatives were validated by direct automatic sequencing. The proband's parents, as well as his brother (born in 2009), are heterozygous carriers of the detected variants (Fig. 1), whereas the proband has these variants in the compound heterozygous state.

Thus, the diagnosis of MPS type IVB in the proband was confirmed by biochemical and molecular genetic methods.

Since the proband and his brother (born in 2009) have grade IV sensorineural hearing loss, but type IVB MPS was ruled out in the brother based on the results of biochemical and molecular genetic studies, additional analysis of exome sequencing data was performed to identify rare variants in the genes associated with isolated hearing loss.

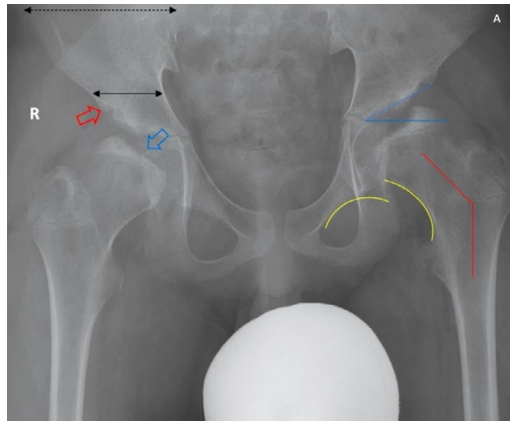

Fig. 4. X-ray image of the hip joints in the frontal view: flattening and impaired ossification of the epiphyses (blue arrow), expansion of the metaphyseal zones, acetabular dysplasia (blue angle), insufficient ossification of the edge of the acetabulum and femoral heads (red arrow), change in the proportions between the width of the wings and body of the ilium (Mickey Mouse sign) (black arrows), valgus deformity of the femoral necks (red line), and discontinuity of Shenton's line (yellow lines)

Two rare variants not previously described in the literature were found in *CDH23* (NM_022124.6). The variant 1 c.6992T>C (p.Val2331Ala) is absent from population databases, is in a highly conserved position, and according to the ACMG classification is regarded by the laboratory that conducted the study as a variant of undefined value. Variant 2 c.805C>T (p.Arg269Trp) is present in databases, with a very low

Table. Results of the study of beta-D-galactosidase activity

Patient	Enzyme activity		Beta-D-galactosidase reference value
	09.11.2020	24.02.2021	
Proband born in 2011	0.72	0.4	2–30 nM/mL/h
Brother born in 2009	3.43	Not tested	
Brother born in 2003	5.57	Not tested	

frequency, and is regarded as an undefined value variant. Pathogenic variants in *CDH23* can be homozygous and compound heterozygous in patients with autosomal recessive deafness type 12 and in patients with Usher syndrome type 1D. Moreover, the patient did not have retinitis pigmentosa, which is characteristic of Usher syndrome, but had severe preverbal hearing loss, which confirmed the diagnosis.

During the validation of these variants by direct automatic sequencing, these variants were noted in the compound heterozygous state in the proband and his brother (born in 2009) and in the heterozygous state in their parents. Having received additional criteria for pathogenicity for these variants, we classified them according to ACMG as probably pathogenic and established a molecular genetic diagnosis of autosomal recessive deafness type 12 associated with *CDH23*.

Thus, detailed molecular genetic, clinical, radiological, and biochemical studies enabled us to diagnose two rare genetic diseases, MPS type IVB and *CDH23*-associated neurosensory deafness.

DISCUSSION

Mucopolysaccharidoses are a group of rare diseases related to lysosomal storage diseases. The first case of MPS was described by Charles Hunter in 1917 [16].

The epidemiology of MPS demonstrates racial and ethnic characteristics in relation to the predominance of one type or another in the population [17]. Thus, in a study conducted from 1984 to 2004 in Taiwan, the total prevalence of MPS was 2.04 per 100,000 live births. Moreover, MPS type II occurred in 52% of cases, type I in 6.0%, type III in 19.0%, type IV in 16%, and type VI in 7.0%. In a Chinese study of 2006–2012 data, type II was also the most common (47.4%), followed by type IVA (26.8%) and type I (16.3%) [18, 19].

According to an American study of 1995–2005 data, MPS type I accounts for 31.7% of cases, type II for 28.3%, type III for 24.2%, type IV for 7.5%, and type VI for 4.2% [20]. In a Canadian study (1969–1996), the proportion of MPS type I was 30%; type IV, 20%; type VI, 15%; type III, 15%; and type II, 5% [21].

Quite often, different MPS types are associated with sensorineural and conductive hearing loss. Thus, MPS type I is characterized by hearing loss in 76.2%–100% of patients [22]. Progressive sensorineural and mixed-type hearing loss has been described in 67.3%–94.0% of patients with MPS type II [23]. Few studies have been conducted regarding the analysis of hearing in patients with MPS type III (A, B, C, and D). This is due to the complexity of audiological screening in this category of patients due to severe cognitive impairment [24]. The degree of hearing loss correlates with the disease subtype, as with MPS type IIID, hearing loss was registered in 25% of patients and in 100% of cases with subtype B [25, 26]. In MPS type IV, hearing loss is associated with subtype A (67.0%–94.0% of patients) [27–29]. Patients with type VI are characterized by conductive hearing loss due to recurrent acute otitis media [30]. In one study, which included 56 patients with MPS type VII, sensorineural hearing loss was detected in 41% of the cases [31]. To date, only four patients with MPS type IX have been described, and none of them had hearing loss [6, 32].

The uniqueness of this clinical case is related to the presence of grade IV sensorineural hearing loss, which is not associated with lysosomal storage diseases. According to the literature, MPS type IVB has not been associated with hearing loss; therefore, another cause of hearing loss in the patient was suspected. Moreover, the proband's brother also has grade IV sensorineural hearing loss; however, he had no clinical and laboratory data of MPS.

In our case, the pathogenic variant c.808T>G in *GLB1* was obtained from the father, and the insertion in the same gene was inherited from the mother, i.e., these variants were detected in the proband in the compound heterozygous state, which determined the clinical presentation of MPS type IVB. Regarding hearing loss, the proband and his brother (born in 2009) inherited both variants, c.6992T>C (p.Val2331Ala) and c.805C>T (p.Arg269Trp) from their mother and father, respectively, which is consistent with the clinical presentation.

Differential diagnostics was primarily performed in bilateral Legg–Calve–Perthes disease. Symmetrical bilateral process, pathognomonic changes in the acetabulum and femoral heads [acetabular dysplasia, insufficient ossification of the acetabular rim and femoral heads, disproportion between the width of the wings and body of the ilium (Mickey Mouse symptom), and valgus deformity of the femoral necks], and a clinical presentation atypical for of Legg–Calve–Perthes disease enabled us to suspect MPS [33].

CONCLUSION

Timely diagnosis of lysosomal storage diseases, including MPS, is necessary for early enzyme replacement therapy, which currently exists for MPS types I, II, IVA, VI, and VII. At an early disease stage, transplantation of hematopoietic stem cells (MPS types I, II, VI, and VII) is also used.

Orthopedic manifestations such as multiple ligamentitis of the hand joints, joint contractures, pathognomonic changes in the epiphyses, and an atypical form of bilateral Legg–Calve–Perthes disease should alert physicians about the presence of MPS.

The determination of enzyme activity in dried blood stains is the simplest and minimally invasive method for diagnosing these diseases, which does not require special training of the patient and medical personnel.

ADDITIONAL INFORMATION

Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Ethical considerations. Written informed consent was obtained from the parents of the proband to conduct molecular genetic testing of blood samples and to publish anonymously the study results.

Author contributions. *V.M. Kenis* performed clinical diagnostics and edited the text. *L.V. Gorobets* and *A.Yu. Dimitrieva* performed clinical diagnostics, literature analysis, and wrote the text. *A.A. Zhmurova-Kriventsova* wrote the text. *I.O. Bychkov* performed molecular genetic and functional analysis and edited the text. *G.V. Baydakova* and *E.Yu. Zakharova* performed biochemical analysis and edited the text. *T.V. Markova* edited the text.

All authors made a significant contribution to the study and preparation of the article, read and approved the final version before its publication.

REFERENCES

1. Wraith JE, Rogers JG, Danks DM. The mucopolysaccharidoses. *J Paediatr Child Health.* 1987;23:329–334. DOI: 10.1111/j.1440-1754.1987.tb00284.x

2. Demydchuk M, Hill CH, Zhou A, et al. Insights into Hunter syndrome from the structure of iduronate-2-sulfatase. *Nat Commun*. 2017;8(1). DOI: 10.1038/ncomms15786

3. Andrade F, Aldámiz-Echevarría L, Llarena M, Couce ML. Sanfilippo syndrome: Overall review. *Pediatr Int*. 2015;57(3):331–338. DOI: 10.1111/ped.12636

4. Shimada T, Tomatsu S, Mason RW, et al. Di-sulfated keratan sulfate as a novel biomarker for mucopolysaccharidosis II, IVA, and IVB. *JIMD Reports*. 2014;21:1–13. DOI: 10.1007/8904_2014_330

5. Tomanin R, Karageorgos L, Zanetti A, et al. Mucopolysaccharidosis type VI (MPS VI) and molecular analysis: Review and classification of published variants in the *ARSB* gene. *Hum Mutat.* 2018;39(12):1788–1802. DOI: 10.1002/humu.23613

6. Natowicz MR, Short MP, Wang Y et al. Clinical and biochemical manifestations of hyaluronidase deficiency. *N Engl J Med*. 1996;335(14):1029–1033. DOI: 10.1056/nejm199610033351405

7. Simonaro CM, Haskins ME, Schuchman EH. Articular chondrocytes from animals with a dermatan sulfate storage disease undergo a high rate of apoptosis and release nitric oxide and inflammatory cytokines: A possible mechanism underlying degenerative joint disease in the mucopolysaccharidoses. *Lab Invest*. 2001;81(9):1319–1328. DOI: 10.1038/labinvest.3780345

8. Wang JY, Roehrl MH. Glycosaminoglycans are a potential cause of rheumatoid arthritis. *Proc Natl Acad Sci USA*. 2002;99(22):14362–14367. DOI: 10.1073/pnas.222536599

9. Simonaro CM, D'Angelo M, He X, et al. Mechanism of glycosaminoglycan-mediated bone and joint disease. *Am J Pathol*. 2008;172(1):112–22. DOI: 10.2353/ajpath.2008.070564

10. Opoka-Winiarska V, Jurecka A, Emeryk A, Tylki-Szymańska A. Osteoimmunology in mucopolysaccharidoses type I, II, VI and VII. Immunological regulation of the osteoarticular system in the course of metabolic inflammation. *Osteoarthritis Cartilage*. 2013;21(12):1813–1823. DOI: 10.1016/j.joca.2013.08.001

11. White KK. Orthopaedic aspects of mucopolysaccharidoses. *Rheumatol*. 2011;50(suppl 5):v26–v33. DOI: 10.1093/rheumatology/ker393

12. Borgo A, Cossio A, Gallone D, et al. Orthopaedic challenges for mucopolysaccharidoses. *Ital J Pediatr*. 2018;44(S2). DOI: 10.1186/s13052-018-0557-y

13. Tomatsu S, Montaño AM, Nishioka T, Orii T. Mucopolysaccharidosis IV (Morquio Syndrome). *Lysosomal Storage Disorders*. 2007:433–445. DOI: 10.1007/978-0-387-70909-3_27

14. Arbisser AI, Donnelly KA, Scott CI, et al. Morquio-like syndrome with beta galactosidase deficiency and normal hexosamine sulfatase activity: Mucopolysaccharidosis IVB. *Am J Med Genet.* 1977;1(2):195–205. DOI: 10.1002/ajmg.1320010205

15. Bychkov I, Kuznetsova A, Baydakova G, et al. Processed pseudogene insertion in GLB1 causes Morquio B disease by altering intronic splicing regulatory landscape. *NPJ genomic medicine*. [in print].

16. Hunter C. A rare disease in two brothers. *Proc R Soc Med.* 1917;10(Study_Dis_Child):104–116. DOI: 10.1177/003591571701001833

17. Zhou J, Lin J, Leung WT, Wang L. A basic understanding of mucopolysaccharidosis: Incidence, clinical features, diagnosis, and management. *Intractable & Rare Diseases Research*. 2020;9(1):1–9. DOI: 10.5582/irdr.2020.01011

18. Lin H-Y, Lin S-P, Chuang C-K, et al. Incidence of the mucopolysaccharidoses in Taiwan, 1984-2004. *Am J Med Genet A*. 2009;149A(5):960–964. DOI: 10.1002/ajmg.a.32781

19. Chen X, Qiu W, Ye J, et al. Demographic characteristics and distribution of lysosomal storage disorder subtypes in Eastern China. *J Hum Genet*. 2016;61(4):345–349. DOI: 10.1038/jhg.2015.155

20. Puckett Y, Bui E, Zelicoff A, Montano A. Epidemiology of mucopolysaccharidoses (MPS) in the United States: challenges and opportunities. *Mol Genet Metab*. 2017;120(1–2):S111. DOI: 10.1016/j.ymgme.2016.11.285

21. Lowry RB, Applegarth DA, Toone JR, et al. An update on the frequency of mucopolysaccharide syndromes in British Columbia. *Hum Genet.* 1990;85(3). DOI: 10.1007/bf00206770

22. Silveira M, Buriti A, Martins A, et al. Audiometric evaluation in individuals with mucopolysaccharidosis. *Clinics*. 2018;73. DOI: 10.6061/clinics/2018/e523

23. Keilmann A, Nakarat T, Bruce IA, et al. Hearing loss in patients with mucopolysaccharidosis II: Data from HOS – the Hunter Outcome Survey. *J Inherit Metab Dis*. 2011;35(2):343–353. DOI: 10.1007/s10545-011-9378-5

24. Valstar MJ, Bertoli-Avella AM, Wessels MW, et al. Mucopolysaccharidosis type IIID: 12 new patients and 15 novel mutations. *Hum Mutat*. 2010;31(5):e1348–1360. DOI: 10.1002/humu.21234

25. Jansen ACM, Cao H, Kaplan P, et al. Sanfilippo syndrome type D. *Archiv Neurology*. 2007;64(11):1629. DOI: 10.1001/archneur.64.11.1629

26. Zafeiriou DI, Savvopoulou-Augoustidou PA, Sewell A, et al. Serial magnetic resonance imaging findings in mucopolysaccharidosis IIIB (Sanfilippo's syndrome B). *Brain Dev*. 2001;23:385–389. DOI: 10.1016/s0387-7604(01)00242-x

27. Lin H-Y, Shih S-C, Chuang C-K, et al. Assessment of hearing loss by pure-tone audiometry in patients with mucopolysaccharidoses. *Mol Genet Metabol*. 2014;111(4):533–538. DOI: 10.1016/j.ymgme.2014.02.003
28. Nagao K, Morlet T, Haley E, et al. Neurophysiology of hearing in patients with mucopolysaccharidosis type IV. *Mol Genet Metabol*. 2018;123(4):472–478. DOI: 10.1016/j.ymgme.2018.02.002
29. Riedner ED, Levin LS. Hearing patterns in Morquio's syndrome (mucopolysaccharidosis IV). *Arch Otolaryngol*. 1977;103:518–520. DOI: 10.1001/archotol.1977.00780260048003
30. Akyol MU, Alden TD, Amartino H, et al. Recommendations for the management of MPS VI: systematic evidence- and consensus-based guidance. *Orphan J Rare Dis*. 2019;14(1). DOI: 10.1186/s13023-019-1080-y
31. Montaño AM, Lock-Hock N, Steiner RD, et al. Clinical course of sly syndrome (mucopolysaccharidosis type VII). *J Med Genet. BMJ*. 2016;53(6):403–418. DOI: 10.1136/jmedgenet-2015-103322
32. Imundo L, LeDuc CA, Guha S, et al. A complete deficiency of Hyaluronoglucosaminidase 1 (HYAL1) presenting as familial juvenile idiopathic arthritis. *J Inher Metab Dis*. 2011;34(5):1013–1022. DOI: 10.1007/s10545-011-9343-3
33. Van den Eeden YNT, Unter Ecker N, Kleinertz H, et al. Total hip arthroplasty in a patient with mucopolysaccharidosis type IVB. *Case Rep Orthop*. 2021;2021:1–8. DOI: 10.1155/2021/5584408

СПИСОК ЛИТЕРАТУРЫ

1. Wraith J.E., Rogers J.G., Danks D.M. The mucopolysaccharidoses // J. Paediatr. Child. Health. 1987. Vol. 23. P. 329–334. DOI: 10.1111/j.1440-1754.1987.tb00284.x
2. Demydchuk M., Hill C.H., Zhou A. et al. Insights into Hunter syndrome from the structure of iduronate-2-sulfatase // Nat. Commun. 2017. Vol. 8. No. 1. DOI: 10.1038/ncomms15786
3. Andrade F., Aldámiz-Echevarría L., Llarena M., Couce M.L. Sanfilippo syndrome: Overall review // Pediatr. Int. 2015. Vol. 57. No. 3. P. 331–338. DOI: 10.1111/ped.12636
4. Shimada T., Tomatsu S., Mason R.W. et al. Di-sulfated keratan sulfate as a novel biomarker for mucopolysaccharidosis II, IVA, and IVB // JIMD Reports. 2014. Vol. 21. P. 1–13. DOI: 10.1007/8904_2014_330
5. Tomanin R., Karageorgos L., Zanetti A. et al. Mucopolysaccharidosis type VI (MPS VI) and molecular analysis: Review and classification of published variants in the *ARSB* gene // Hum. Mutat. 2018. Vol. 39. No. 12. P. 1788–1802. DOI: 10.1002/humu.23613
6. Natowicz M.R., Short M.P., Wang Y. et al. Clinical and biochemical manifestations of hyaluronidase deficiency // N. Engl. J. Med. 1996. Vol. 335. No. 14. P. 1029–1033. DOI: 10.1056/nejm199610033351405
7. Simonaro C.M., Haskins M.E., Schuchman E.H. Articular chondrocytes from animals with a dermatan sulfate storage disease undergo a high rate of apoptosis and release nitric oxide and inflammatory cytokines: A possible mechanism underlying degenerative joint disease in the mucopolysaccharidoses // Lab. Invest. 2001. Vol. 81. No. 9. P. 1319–1328. DOI: 10.1038/labinvest.3780345
8. Wang J.Y., Roehrl M.H. Glycosaminoglycans are a potential cause of rheumatoid arthritis // Proc. Natl. Acad. Sci. USA. 2002. Vol. 99. No. 22. P. 14362–13367. DOI: 10.1073/pnas.222536599
9. Simonaro C.M., D'Angelo M., He X. et al. Mechanism of glycosaminoglycan-mediated bone and joint disease // Am. J. Pathol. 2008. Vol. 172. No. 1. P. 112–122. DOI: 10.2353/ajpath.2008.070564
10. Opoka-Winiarska V., Jurecka A., Emeryk A., Tylki-Szymańska A. Osteoimmunology in mucopolysaccharidoses type I, II, VI and VII. Immunological regulation of the osteoarticular system in the course of metabolic inflammation // Osteoarthritis Cartilage. 2013. Vol. 21. No. 12. P. 1813–1823. DOI: 10.1016/j.joca.2013.08.001
11. White K.K. Orthopaedic aspects of mucopolysaccharidoses // Rheumatol. 2011. Vol. 50. Suppl. 5. P. v26–v33. DOI: 10.1093/rheumatology/ker393
12. Borgo A., Cossio A., Gallone D. et al. Orthopaedic challenges for mucopolysaccharidoses // Ital. J. Pediatr. 2018. Vol. 44. No. S2. DOI: 10.1186/s13052-018-0557-y
13. Tomatsu S., Montaño A.M., Nishioka T., Orii T. Mucopolysaccharidosis IV (Morquio Syndrome) // Lysosomal Storage Disorders. 2007. P. 433–445. DOI: 10.1007/978-0-387-70909-3_27
14. Arbisser A.I., Donnelly K.A., Scott C.I. et al. Morquio-like syndrome with beta galactosidase deficiency and normal hexosamine sulfatase activity: Mucopolysaccharidosis IVB // Am. J. Med. Genet. 1977. Vol. 1. No. 2. P. 195–205. DOI: 10.1002/ajmg.1320010205
15. Bychkov I., Kuznetsova A., Baydakova G. et al. Processed pseudogene insertion in GLB1 causes Morquio B disease by altering intronic splicing regulatory landscape // NPJ Genom. Med. [in print].
16. Hunter C. A rare disease in two brothers // Proc. R. Soc. Med. 1917. Vol. 10. (Study_Dis_Child). P. 104–116. DOI: 10.1177/003591571701001833
17. Zhou J., Lin J., Leung W.T., Wang L. A basic understanding of mucopolysaccharidosis: Incidence, clinical features, diagnosis, and management // Intractable & Rare Diseases Research. 2020. Vol. 9. No. 1. P. 1–9. DOI: 10.5582/irdr.2020.01011
18. Lin H.-Y., Lin S.-P., Chuang C.-K. et al. Incidence of the mucopolysaccharidoses in Taiwan, 1984-2004 // Am. J. Med. Genet. A. 2009. Vol. 149A. No. 5. P. 960–964. DOI: 10.1002/ajmg.a.32781
19. Chen X., Qiu W., Ye J. et al. Demographic characteristics and distribution of lysosomal storage disorder subtypes in Eastern China // J. Hum. Genet. 2016. Vol. 61. No. 4. P. 345–349. DOI: 10.1038/jhg.2015.155
20. Puckett Y., Bui E., Zelicoff A., Montano A. Epidemiology of mucopolysaccharidoses (MPS) in the United States: challenges and opportunities // Mol. Genet. Metab. 2017. Vol. 120. No. 1–2. P. S111. DOI: 10.1016/j.ymgme.2016.11.285
21. Lowry R.B., Applegarth D.A., Toone J.R. et al. An update on the frequency of mucopolysaccharide syndromes in British Columbia // Hum. Genet. 1990. Vol. 85. No. 3. DOI: 10.1007/bf00206770
22. Silveira M., Buriti A., Martins A. et al. Audiometric evaluation in individuals with mucopolysaccharidosis // Clinics. 2018. Vol. 73. DOI: 10.6061/clinics/2018/e523
23. Keilmann A., Nakarat T., Bruce I.A. et al. Hearing loss in patients with mucopolysaccharidosis II: Data from HOS – the Hunter Outcome Survey // J. Inherit. Metab. Dis. 2011. Vol. 35. No. 2. P. 343–353. DOI: 10.1007/s10545-011-9378-5

24. Valstar M.J., Bertoli-Avella A.M., Wessels M.W. et al. Mucopolysaccharidosis type IIID: 12 new patients and 15 novel mutations // Hum. Mutat. 2010. Vol. 31. No. 5. P. e1348–1360. DOI: 10.1002/humu.21234
25. Jansen A.C.M., Cao H., Kaplan P., et al. Sanfilippo syndrome type D // Archiv. Neurology. 2007. Vol. 64. No. 11. P. 1629. DOI: 10.1001/archneur.64.11.1629
26. Zafeiriou D.I., Savvopoulou-Augoustidou P.A., Sewell A. et al. Serial magnetic resonance imaging findings in mucopolysaccharidosis IIIB (Sanfilippo's syndrome B) // Brain Dev. 2001. Vol. 23. P. 385–389. DOI: 10.1016/s0387-7604(01)00242-x
27. Lin H.-Y., Shih S.-C., Chuang C.-K. et al. Assessment of hearing loss by pure-tone audiometry in patients with mucopolysaccharidoses // Mol. Genet. Metab. 2014. Vol. 111. No. 4. P. 533–538. DOI: 10.1016/j.ymgme.2014.02.003
28. Nagao K., Morlet T., Haley E. et al. Neurophysiology of hearing in patients with mucopolysaccharidosis type IV // Mol. Genet. Metab. 2018. Vol. 123. No. 4. P. 472–478. DOI: 10.1016/j.ymgme.2018.02.002
29. Riedner E.D., Levin L.S. Hearing patterns in Morquio's syndrome (mucopolysaccharidosis IV) // Arch. Otolaryngol. 1977. Vol. 103. P. 518–520. DOI: 10.1001/archotol.1977.00780260048003
30. Akyol M.U., Alden T.D., Amartino H. et al. Recommendations for the management of MPS VI: systematic evidence- and consensus-based guidance // Orphan. J. Rare Dis. 2019. Vol. 14. No. 1. DOI: 10.1186/s13023-019-1080-y
31. Montaño A.M., Lock-Hock N., Steiner R.D. et al. Clinical course of sly syndrome (mucopolysaccharidosis type VII) // BMJ. 2016. Vol. 53. No. 6. P. 403–418. DOI: 10.1136/jmedgenet-2015-103322
32. Imundo L., LeDuc C.A., Guha S. et al. A complete deficiency of Hyaluronoglucosaminidase 1 (HYAL1) presenting as familial juvenile idiopathic arthritis // J. Inherit. Metab. Dis. 2011. Vol. 34. No. 5. P. 1013–1022. DOI: 10.1007/s10545-011-9343-3
33. Van den Eeden Y.N.T., Unter Ecker N., Kleinertz H. et al. Total hip arthroplasty in a patient with mucopolysaccharidosis type IVB // Case Rep. Orthop. 2021. Vol. 2021. P. 1–8. DOI: 10.1155/2021/5584408

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