THE VERTEBRAL SYNDROME IN VARIOUS TYPES OF MUCOPOLYSACCHARIDOSIS: CLINICAL FEATURES AND TREATMENT

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The paper presents recommendations on the assessment and treatment of vertebral pathology in patients with various types of mucopolysaccharidosis. The recommendations are based on literature data and the authors' own experience. The purpose of the publication is an invitation to the discussion in the format of an expert consensus.

Key Words: mucopolysaccharidosis, vertebral syndrome, spinal patalogy.

Please cite this paper as: *Ryabykh SO, Ochirova PV, Gubin AV, Kolesov SV, Kolbovsky DA, Tretjakova AN, Ryabykh TV, Medvedeva SN, Savin DM, Burtsev AV, Saifutdinov MS. The vertebral syndrome in various types of mucopolysaccharidosis: clinical features and treatment. Hir. Pozvonoc. 2019;16(2):81–91. In Russian. DOI: http://dx.doi.org/10.14531/ss2019.2.81-91.*

The opportunities of targeted therapy have attracted attention not only to mucopolysaccharidosis (MPS) but also to growing trends in improving the quality of life, in particular due to timely neurosurgical and orthopedic interventions.

More than a year and a half has passed since the establishment of an inter-rater group for treating MPS patients within the Association of Traumatologists and Orthopedists of Russia. Now, it is time to review the preliminary results.

We briefly describe the main tasks faced by the group's experts:

1) recruitment of a multidisciplinary team of experts (geneticists, pediatricians, general practitioners, orthopedists, neurosurgeons, anesthesiologists, neurologists, rehabilitation physicians) to assess the syndromic status of the entire nosologic group and a particular patient; substantiation of rehabilitation approaches, including the surgical one;

2) preparation of a federal clinical guidelines draft;

3) coordination of interdisciplinary patient logistics;

4) planning of multicenter and survey studies based on intra- and inter-rater assessment.

At the 11th All-Russian Congress of Traumatologists and Orthopedists of Russia held in Saint-Petersburg, April 11–13, 2018, there was a second round table discussion on syndromic assessment of the status of MPS patients and aspects of early diagnosis and approaches in treatment of the orthopedic pathology. The presented paper is the first product of the expert group. The authors will gratefully welcome all comments and suggestions.

General methodology of guidelines

The clinical guidelines on the diagnosis and treatment of spinal pathology in different MPS types were developed by a group of experts based on the evidence-based medicine principles. Information was searched in the Medline (Pubmed version), Embase (Dialog version), and Cochrane Library electronic databases, based on a systematic review of the literature, using, in particular, a consensus of study's author opinions.

MPS belongs to the group of orphan diseases, which excludes large cohort and randomized studies; therefore, only expert opinions published within the last two decades can be used to develop protocols for the diagnosis and treatment of spinal disease.

Design

An analysis of publications devoted to this problem demonstrated that almost all of the publications were based on series of clinical cases. No studies that might be attributed to an ASMOK (Association of Medical Societies for Quality of Medical Care and Education) level exceeding 2+ and to I or II evidence level were found. Accordingly, all guidelines in this document are of evidence level C or less.

The purpose of this study is to develop the algorithm for treatment of vertebral syndrome in patients with different types of MPS.

The paper is presented mainly in the form of tables for the most vivid presentation of the material. We have already used this form, and, in our opinion, it is very convenient for perception and practical application. The features of selection and analysis of the material are deliberately not considered in the presented guidelines.

Methods used to assess the quality and strength of evidence are as follows:

– consensus of experts;

– assessment of the evidence level in accordance with a rating scheme (Table 1).

Definitions and classification

MPS is a group of complex heterogeneous progressive diseases caused by deficiency of lysosomal enzymes involved in the glycosaminoglycan degradation pathway [1]. Depending on the deficiency in one of the 11 lysosomal enzymes (chondroitin sulfate, dermatan sulfate, heparan sulfate, keratan sulfate, and/or hyaluronate), seven main MPS types are distinguished (Table 2). The manifestations are associated with impaired utilization and accumulation of glycosaminoglycans in lysosomes of cells in all organs [2]. According to the international classification of hereditary skeletal diseases [3], all MPS types belong to the group of lysosomal storage diseases involving the skeleton (multiple dysostosis).

Multisystem phenotypic symptoms. Products of abnormal metabolism cause physical development delay, coarsening of facial features, mental retardation, skeletal dysplasia, hepatosplenomegaly, frequent respiratory infections leading to respiratory failure, cardiovascular disorders, eye diseases, hard hair growth, and changes in the skin [4, 5]. All MPS types, except for, probably, MPS III, are associated with these somatic symptoms.

Neurocognitive disorders (including mental deficiency, adaptive behavior and motor skill learning, impaired attention and memory, delayed speech development), which are usually associated with sleep disorders and epileptic seizures that often occur in MPS III, can also be observed in patients with MPS I, II, and VII [6].

Secondary neurological symptoms, often in the form of motor deficit, develop in the following cases [7–10]:

1) in stenosis at the foramen magnum level with spinal cord compression, hydrocephalus, and Chiari I malformation;

2) in kyphotic (kyphoscoliotic) deformity of the thoracolumbar spine, often resulting in vertebromedullary conflict;

3) in peripheral nerve lesions associated with tunnel syndromes (the most common manifestation is carpal tunnel syndrome).

Treatment of these symptoms usually involves surgery. The clinical and radiological features of vertebral syndrome in MPS are as follows [17–25]:

– underdevelopment of the axial muscles;
– increased physiological kyphosis;
– disc protrusion, anterior disc herniation;
– hypoplasia, wedging of the apical vertebrae;
– hypermobility of spinal motion segments;
– progressive kyphosis/kyphoscoliosis at the thoracolumbar junction level;
– cervical stenosis (untypical of MPS type III and VII).

The clinical and radiological features of cervical stenosis in MPS are as follows:

– laminar hypoplasia (especially in C1);
– thickening of soft tissues in the craniovertebral junction area (dura mater, ligaments, cellular tissue);
– dysplasia/hypoplasia, odontoid retroflexion;
– C1–C2 instability;
– true spinal stenosis;
– foramen magnum stenosis;
– spinal cord compression;
– disc protrusion;
– syringomyelia, Arnold-Chiari I malformation;
– combination of factors.

Dysplasia/hypoplasia, odontoid retroflection, and C1–C2 instability cause segmental instability [8, 10, 16–18, 26–28].

A review of spinal changes in MPS, which are able to cause secondary neurological manifestations, is presented in Table 3.

The objectives and basic principles of conservative treatment of children with different MPS types are presented in Table 4.

The follow-up protocol for patients with MPS is provided in Table 5.

The system for assessment of cervical spinal cord compression to determine the indications for surgery in patients with MPS type VI, based on the clinical neurological status, somatosensory

Table 1
The rating scheme for assessment of the publication value

Level of evidence	Characteristics
A	High-quality meta-analysis, a systematic review of RCTs, or very large RCTs with a very low probability of systematic error, the results of which can be extended to the relevant Russian population
B	A high-quality review, or a systematic review of cohort studies, or a case-control study, or a high-quality cohort study, or a case-control study with a very low level of systematic error, or RCTs with a low risk of systematic error, the results of which can be extended to the relevant Russian population
C	A cohort study, or a case-control study, or a controlled study without randomization with a low level of systematic error, the results of which can be extended to the relevant Russian population, or RCTs with a (very) low risk of systematic error, the results of which cannot be extended to the relevant Russian population
D	Case series report, or an uncontrolled study, or an expert opinion

RCT – randomized clinical trial.

Table 2
Orthopedic manifestations of pathology depending on the type of mucopolysaccharidosis (MPS) [8, 10–17]

Type/syndrome	Clinical manifestations
MPS I/Hurler	Multiple dysostosis, disproportionate dwarfism, multiple contractures in joints, carpal canal syndrome, os odontoideum, atlantoaxial instability, acetabular dysplasia, *coxa valga bilateralis, genu valgum*, stenosing ligamentitis
MPS I/Hurler-Scheie, Scheie	More mild manifestations of Hurler syndrome
MPS II/Hunter	Multiple dysostosis, disproportionate dwarfism, multiple contractures in joints, carpal canal syndrome, os odontoideum, atlantoaxial instability, acetabular dysplasia, *coxa valga bilateralis, genu valgum*, stenosing ligamentitis
MPS III/Sanfilippo	Only mild somatic manifestations, subnanism, moderate contractures (mainly in the elbow joints)
MPS IV/Morquio	Severe skeletal dysplasia, multiple dysostosis, disproportionate dwarfism, hypermobility of joints, os odontoideum, atlantoaxial instability, *coxa valga bilateralis*, acetabular dysplasia with impaired hip joint relationships, *genus valgum*, foot deformities, chest deformities
MPS VI/Maroto-Lamy	Multiple dysostosis, disproportionate dwarfism, contractures in joints, carpal canal syndrome, os odontoideum, atlantoaxial instability, acetabular dysplasia, *coxa valga bilateralis*, *genu valgum*, stenosing ligamentitis, chest deformity
MPS VII/Sly	Multiple dysostosis, disproportionate dwarfism, contractures in joints, os odontoideum, atlantoaxial instability, acetabular dysplasia, chest deformity
MPS IX/hyaluronidase deficiency	Subnanism, periarticular hypertrophy, nodular synovial masses with effusion in joints, acetabular erosion

evoked potentials of the median nerve, and MRI findings for the craniocervical junction is presented in Table 6. An overall score of > 3 is an indication for surgical decompression.

The objectives and basic principles of surgical treatment of children with different MPS types are as follows:

– reversal and prevention of neurological deficit (elimination of stenosis and/or instability at the C1–C2 level, correction of kyphoscoliosis) [40–44];

– prevention of respiratory disorders (correction of kyphoscoliosis) [40, 45–50];

– maintenance of the walking ability (correction of lower limb deformity and contractures) [49, 51–57];

– improvement or preservation of the functional, orthopedic, and neurological status of patients [40–44, 46–47, 50, 52–54, 57–58];

– improvement of the life quality (elimination of body imbalance/carpal canal stenosis) [40–50, 59–60];

– increase in the life span [40–44, 46–47, 50, 53–54, 57–60].

The basic principles and surgical treatment approach for spinal pathology in MPS are presented in Tables 7 and 8.

Fig. 1 shows the surgical treatment approach for spinal pathology in patients with different types of MPS. Surgical correction of spinal pathology in MPS is performed with allowance for the features of vertebral syndrome (Table 9).

Limitations to the use of guidelines for surgical treatment of spinal pathology in MPS

The main purpose of the described approaches is to preserve the patient's motor activity, quality of life, and social adaptation. Therefore, the main contraindications to complexity of positioning with head fixation application of the guidelines include:

– decompensated concomitant pathology, including that caused by the underlying disease, which is life-threatening or having significant limitations for the expected survival period;

– communication gap with parents regarding the goal of an oriented treatment strategy;

– infectious processes in the exacerbation period.

Conclusion

Spinal pathology is one of the leading syndromic manifestations of MPS. The spinal dysmorphism syndrome complex includes three typical syndromes: stenosis of the craniocervical junction, most typical of MPS type I, II, and VI; craniocervical instability (which is often combined with stenosis) in MPS type IV; and kyphosis/kyphoscoliosis in MPS type I, IV, and VI.

A key component of early screening for vertebral syndrome is assessment of the patient's neurological and motor status. The most accepted tools are the modified scale of the Japanese Orthopedic Association (mJOA), Nurick scale, 6-minute walk test, and 3-minute stair climb test.

Deterioration of the neurological status and quality of life in the setting of confirmed stenosis and instability as well as progression of spinal deformity underlie prognostically vital indications for surgical correction.

Decompression and occipital-cervical fusion are indicated in patients with instability and stenosis at the craniovertebral junction level.

Stable segment-by-segment fixation of the spine is indicated for local kyphotic/kyphoscoliotic curves, within five spinal motion segments.

Spinal fixation by dynamic systems is preferable for extended spinal deformities.

The guidelines do not concern the possibility of age and interdisciplinary continuity, detailed planning of the treatment approach with assessment of a perioperative risk, and desire to solve orthopedic and neurosurgical tasks within one session. These circumstances underlie the need for multidisciplinary and multicenter studies.

The study was conducted without financial support.
The authors declare no conflict of interest.

Table 3

Spinal changes in mucopolysaccharidosis (MPS) [17–25, 29–30]

Type of MPS/syndrome	Craniovertebral stenosis	Occipital-cervical instability	Thoracolumbar kyphosis	Scoliosis
MPS I/Hurler	++*	+	++	+
MPS I/Hurler-Scheie, Scheie	++	–	+	+
MPS II/Hunter	++	–	+	
MPS IV/Morquio	+	+++	++	+
MPS VI/Maroto-Lamy	+++	+	++	+

– absent; + rare; ++ ordinary; +++ often.

* Without bone marrow transplantation (+ for patients after transplantation of hematopoietic stem cells).

Table 4

Objectives and basic principles of conservative treatment of children with different types of mucopolysaccharidosis [31–34]

Improvement of neurological condition*	Anticholinesterase drugs, anticonvulsants, dehydration. Currently, there is no effective treatment of neurological complications
Improvement of orthopedic status	Corset therapy, massage, exercise therapy, orthotics, orthopedic correction of pathological arrangements, contractures, etc.
Social adaptation**	Physical and functional rehabilitation, training to use assistive devices – verticalizers, braces, devices

* The most valid tools for assessing the neurological status of patients with different types of mucopolysaccharidosis are the modified scale of the Japanese Orthopedic Association (mJOA), Nurick scale, 6-minute walk test, and 3-minute stair climb test.

** Scored integrative assessment of disabilities and role limitations is often performed using the Functional Independence Measure (FIM) scale.

Table 5

The recommended protocol to follow-up patients with different types of mucopolysaccharidosis [8, 17, 36–39]

Examination	Examination rate
Clinical examination by a neurologist and an orthopedist	6 months
X-ray of the cervical spine (upright and lateral projections, flexion, extension)	2 to 3 years
X-ray of the thoracic and lumbar spine with involvement of the hip joints (upon progression)	2 to 3 years (every 6 months)
MRI of the cerebral and spinal conductive pathways (tractography, if possible)	1 year
Functional MRI of the cervical spine with flexion and extension	1–3 years
CT of the craniovertebral junction + cervical + thoracic + lumbar spine + CT of the upper respiratory tract and lungs	Before surgery

Table 6

The system for assessment of spinal cord compression at the craniovertebral junction level to decide the need for surgical treatment [35]

Score	Test results
Clinical neurological examination	
0	– normal neurological findings;
1	– increased/decreased tendon reflexes, lateral differences in muscle reflexes;
2	– pyramidal tract signs: Babinski reflex, Gordon reflex, Oppenheim reflex, muscle twitching;
3	– paresis or weakness of the upper and/or lower limbs
Somatosensory evoked potentials of the median nerve	
0	– normal;
1	– prolongation of at least one of the interpeak latencies: N9/P13, N9/N13b, or N13a/N20 (> 2.5 SD)*;
2	– lack of P13 and/or N13b (subcortical);
3	– lack of N20 (cortical)
MRI	
0	– no spinal cord compression;
1	– spinal cord compression (no CSF in any direction);
3	– myelomalacia signs

* N9/P13: brachial plexus – caudate nucleus; N9/N13b: brachial plexus – caudate nucleus; N13a/N20: caudal spinal cord – cortex.

Table 7

Basic principles of surgical treatment of spinal pathology associated with different types of mucopolysaccharidosis [40–50]

Surgical treatment principles	Indications
Decompression and stabilization	Stenosis, instability, and stenosis combined with instability at the craniovertebral junction level, mechanical neurological instability
Deformity correction with instrumented stabilization of the spine	Progression of spinal deformity, worsening of somatic and neurological statuses

Table 8

Surgical treatment approach for spinal pathology in mucopolysaccharidosis [22, 46–47, 50, 61–62]

Spine region	Deformity correction	Spinal cord decompression
Cervical	+/–	+
Thoracic	+	+/–
Lumbar	+	–

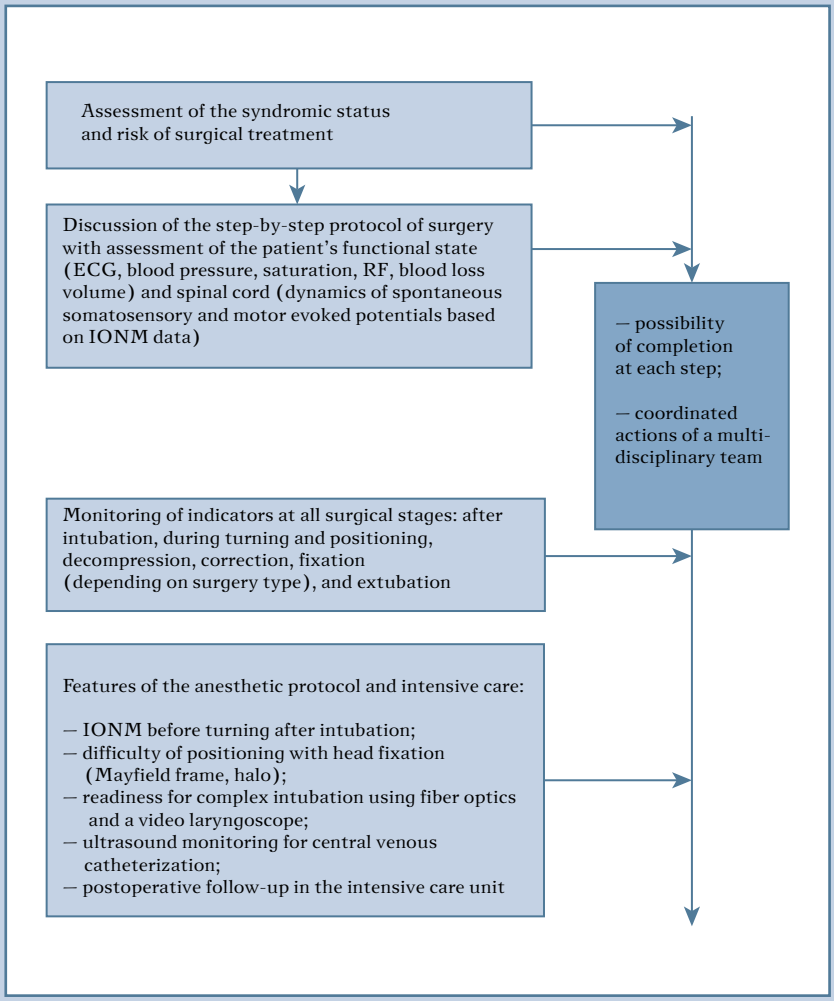

Fig. 1
Surgical treatment approach for spinal pathology in patients with different types of mucopolysaccharidosis [63–66]: RF – respiratory function; IONM – intraoperative neuromonitoring

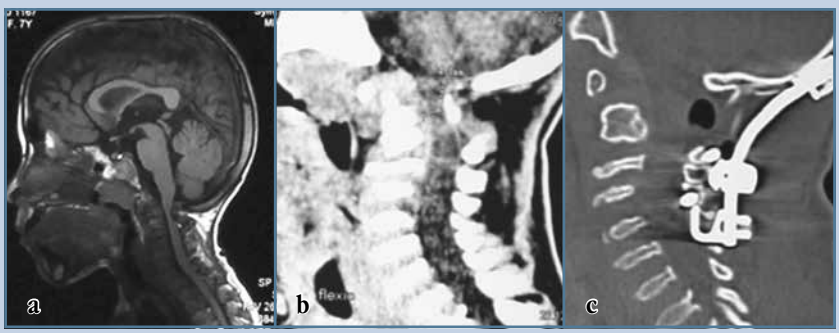

Fig. 2
MRI (a) and CT scans before (b) and after (c) surgery in a 6-year-old child with cervical stenosis associated with mucopolysaccharidosis type IV (Morquio A): spastic tetraparesis

Таблица 9

Variants of surgical correction for spinal pathology with allowance for vertebral syndrome features

Spinal pathology	Features of orthopedic correction
Instability, stenosis, and combination of instability and stenosis at the craniovertebral junction level; foci of myelopathy *(Fig. 2)*	Decompression and posterior instrumented fixation (occipital-cervical fusion)
Local (no more than five spinal motion segments) spinal deformities, local kyphosis of more than 20°, and scoliosis of more than 40° *(Fig. 3)*	Stable segmental fixation of the spine
Extensive (more than five spinal motion segments) spinal deformities, kyphosis of more than 20°, and scoliosis of more than 40° *(Fig. 4)*	Dynamic spine fixation

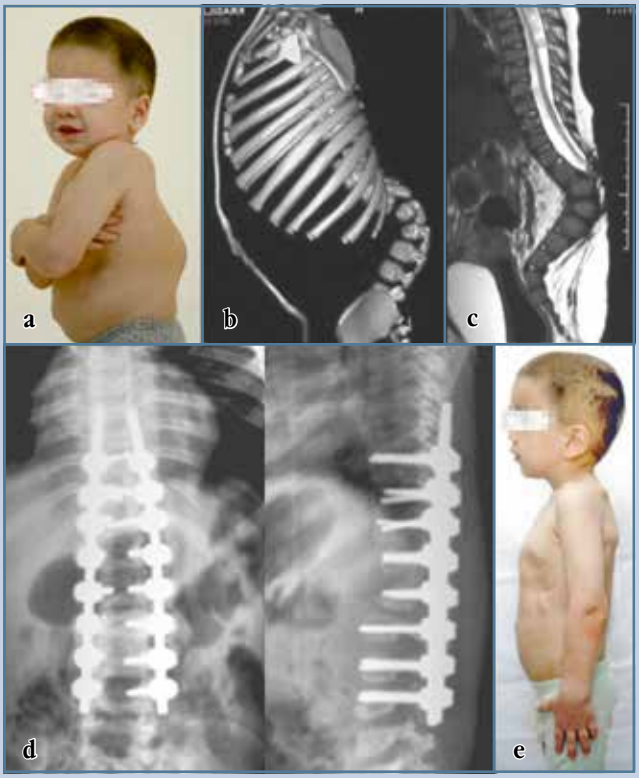

Fig. 3
Appearance and radiological findings of a 3-year-old child with kyphosis associated with mucopolysaccharidosis type IH: **a** – before surgery; **b** – structural changes in the apical vertebral bodies; **c** – signs of spinal cord compression; **d** – after correction and instrumented fixation of deformity at the T9–L4 level; **e** – after surgery

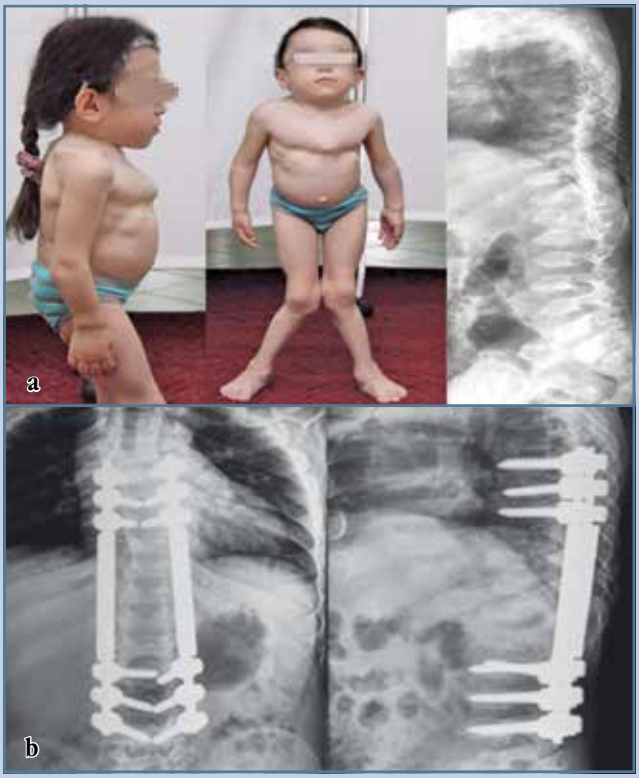

Fig. 4
Appearance and radiological findings of a 6-year-old child with scoliotic deformity associated with mucopolysaccharidosis type IVA: **a** – before surgery; **b** – after correction and posterior instrumented dynamic fixation of deformity at the T5–L2 level

References

1. **Muenzer J.** Overview of the mucopolysaccharidoses. Rheumatology (Oxford). 2011;50 Suppl 5:v4–v12. DOI: 10.1093/rheumatology/ker394.
2. **Clarke LA.** Mucopolysaccharidosis Type I. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews(R) [Internet]. Seattle (WA): University of Washington, Seattle, 1993–2019. 2002 Oct 31 [updated 2016 Feb 11].
3. **Bonafe L, Cormier-Daire V, Hall C, Lachman R, Mortier G, Mundlos S, Nishimura G, Sangiorgi L, Savarirayan R, Sillence D, Spranger J, Superti-Furga A, Warman M, Unger S.** Nosology and classification of genetic skeletal disorders: 2015 revision. Am J Med Genet A. 2015;167A:2869–2892. DOI: 10.1002/ajmg.a.37365.
4. **Leone A, Rigante D, Amato DZ, Casale R, Pedone L, Magarelli N, Colosimo C.** Spinal involvement in mucopolysaccharidoses: a review. Childs Nerv Syst. 2015;31:203–212. DOI: 10.1007/s00381-014-2578-1.
5. **Muenzer J, Beck M, Eng CM, Escolar ML, Giugliani R, Guffon NH, Harmatz PR, Kamin W, Kampmann C, Koseoglu ST, Link B, Martin RA, Molter DW, Munoz Rojas MV, Ogilvie JW, Parini R, Ramaswami U, Scarpa M, Schwartz IV, Wood RE, Wraith EH.** Multidisciplinary management of Hunter syndrome. Pediatrics. 2009;124:e1228–e1239. DOI: 10.1542/peds.2008-0999.
6. **Shapiro EG, Jones SA, Escolar ML.** Developmental and behavioral aspects of mucopolysaccharidoses with brain manifestations – Neurological signs and symptoms. Mol Genet Metab. 2017;122S:1–7. DOI: 10.1016/j.ymgme.2017.08.009.
7. **White KK, Sousa TM.** Mucopolysaccharide disorders in orthopaedic surgery. J Am Acad Orthop Surg. 2012;21:12–22. DOI: 10.5435/JAAOS-21-01-12.
8. **Lachman R, Martin KW, Castro S, Basto MA, Adams A, Teles EL.** Radiologic and neuroradiologic findings in the mucopolysaccharidoses. J Pediatr Rehabil Med. 2010;3:109–118. DOI: 10.3233/PRM-2010-0115.
9. **White K, Kim T, Neufeld JA.** Clinical assessment and treatment of carpal tunnel syndrome in the mucopolysaccharidoses. J Pediatr Rehabil Med. 2010;3:57–62. DOI: 10.3233/PRM-2010-0103.
10. **Zafeiriou DI, Batzios SP.** Brain and spinal MR imaging findings in mucopolysaccharidoses: a review. AJNR Am J Neuroradiol. 2013;34(1):5–13. DOI: 10.3174/ajnr.A2832.
11. **Lehman TJA, Miller N, Norquist B, Underhill L, Keutzer J.** Diagnosis of the mucopolysaccharidoses. Rheumatology (Oxford). 2011;50 Suppl 5:v41–v48. DOI: 10.1093/rheumatology/ker390.
12. **Neufeld EF, Muenzer J.** The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW, Vogelstein B, eds. The Online Metabolic and Molecular Bases of Inherited Disease, 8th ed. New York: McGraw-Hill Medical Publishing Division, 2001:3421–3452. DOI: 10.1036/ommbid.165.
13. **Montano AM, Tomatsu S, Gottesman GS, Smith M, Orii T.** International Morquio A Registry: clinical manifestation and natural course of Morquio A disease. J Inherit Metab Dis. 2007;30:165–174. DOI: 10.1007/s10545-007-0529-7.
14. **Giugliani R.** Mucopolysacchariddoses: from understanding to treatment, a century of discoveries. Genet Mol Biol. 2012;35(4 Suppl):924–931. DOI: 10.1590/S1415-47572012000600006.
15. **Rigante D.** Gargoyle-like features in lysosomal diseases involving glycosaminoglycans. Childs Nerv Syst. 2007;23:365–366. DOI: 10.1007/s00381-007-0301-1.
16. **Rasalkar DD, Chu WC, Hui J, Chu CM, Paunipagar BK, Li C-**K. Pictorial review of mucopolysaccharidosis with emphasis on MRI features of brain and spine. Br J Radiol. 2011;84:469–477. DOI: 10.1259/bjr/59197814.
17. **Solanki GA, Martin KW, Theroux MC, Lampe C, White KK, Shediac R, Lampe CG, Beck M, Mackenzie WG, Hendriksz CJ, Harmatz PR.** Spinal involvement in mucopolysaccharidosis IVA (Morquio-Brailsford or Morquio A syndrome): presentation, diagnosis and management. J Inherit Metab Dis. 2013;36:339–355. DOI: 10.1007/s10545-013-9586-2.
18. **Swischuk LE.** The beaked, notched, or hooked vertebra: its significance in infants and young children. Radiology. 1970;95:661–664. DOI: 10.1148/95.3.661.
19. **Field RE, Buchanan JA, Copplemans MG, Aichroth PM.** Bone-marrow transplantation in Hurler's syndrome. Effect on skeletal development. J Bone Joint Surg Br. 1994;76:975–981.
20. **Vinchon M, Cotten A, Clarisse J, Chiki R, Christiaens JL.** Cervical myelopathy secondary to Hunter syndrome in an adult. AJNR Am J Neuroradiol. 1995;16:1402–1403.
21. **Langer LO Jr, Carey LS.** The roentgenographic features of the KS mucopolysaccharidosis of Morquio (Morquio-Brailsford's disease). Am J Roentgenol Radium Ther Nucl Med. 1966;97:1–20. DOI: 10.2214/ajr.97.1.1.
22. **Tandon V, Williamson JB, Cowie RA, Wraith JE.** Spinal problems in mucopolysaccharidosis I (Hurler syndrome). J Bone Joint Surg Br. 1996;78:938–944. DOI: 10.1302/0301-620X78B6.1279.
23. **Berlemann U, Jeszenszky DJ, Buhler DW, Harms J.** Mechanisms of retrolisthesis in the lower lumbar spine. A radiographic study. Acta Orthop Belg. 1999;65:472–477.
24. **Leone A, Guglielmi G, Cassar-Pullicino VN, Bonomo L.** Lumbar intervertebral instability: a review. Radiology. 2007;245:62–77. DOI: 10.1148/radiol.2451051359.
25. **Levin TL, Berdon WE, Lachman RS, Anyane-Yeboa K, Ruzal-Shapiro C, Roye DP Jr.** Lumbar gibbus in storage diseases and bone dysplasias. Pediatr Radiol. 1997;27:289–294. DOI: 10.1007/s002470050131.
26. **Thorne JA, Javadpour M, Hughes DG, Wraith E, Cowie RA.** Craniovertebral abnormalities in Type VI mucopolysaccharidosis (Maroteaux-Lamy syndrome). Neurosurgery. 2001;48:849–852. DOI: 10.1097/00006123-200104000-00031.
27. **Vougioukas VI, Berlis A, Kopp MV, Korinthenberg R, Spreer J, van Velthoven V.** Neurosurgical interventions in children with Maroteaux-Lamy syndrome. Case report and review of the literature. Pediatr Neurosurg. 2001;35:35–38. DOI: 10.1159/000050383.
28. **Rigante D, Antuzzi D, Ricci R, Segni G.** Cervical myelopathy in mucopolysaccharidosis type IV. Clin Neuropathol. 1999;18:84–86.
29. **Mut M, Cila A, Varli K, Akalan N.** Multilevel myelopathy in Maroteaux-Lamy syndrome and review of the literature. Clin Neurol Neurosurg. 2005;107:230–235. DOI: 10.1016/j.clineuro.2004.05.003.
30. **Tong CKW, Chen JC, Cochrane DD.** Spinal cord infarction remote from maximal compression in a patient with Morquio syndrome. J Neurosurg Pediatr. 2012;9:608–612. DOI: 10.3171/2012.2.PEDS11522.
31. **Nurick S.** The pathogenesis of the spinal cord disorder associated with cervical spondylosis. Brain. 1972;95:87–100. DOI: 10.1093/brain/95.1.87.
32. **Lammers AE, Hislop AA, Flynn Y, Haworth SG.** The 6-minute walk test: normal values for children of 4–11 years of age. Arch Dis Child. 2008;93(6):464–468. DOI: 10.1136/adc.2007.123653.
33. **Harmatz P, Mengel KE, Giugliani R, Valayannopoulos V, Lin SP, Parini R, Guffon N, Burton BK, Hendriksz CJ, Mitchell J, Martins A, Jones S, Guelbert N, Vellodi A, Hollak C, Slasor P, Decker C.** The Morquio A Clinical Assessment Program: baseline results illustrating progressive, multisystemic clinical impairments in Morquio A subjects. Mol Genet Metab. 2013;109:54–61. DOI: 10.1016/j.ymgme.2013.01.021.
34. **Harmatz P, Ketteridge D, Giugliani R, Guffon N, Teles EL, Miranda MC, Yu ZF, Swiedler SJ, Hopwood JJ.** Direct comparison of measures of endurance, mobility, and joint function during enzyme-replacement therapy of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): results after 48 weeks in a phase 2 open-label clinical study of recombinant human N-acetylgalactosamine 4-sulfatase. Pediatrics. 2005;115:e681–e689. DOI: 10.1542/peds.2004-1023.

35. **Alden TD, Amartino H, Dalla Corte A, Lampe C, Harmatz PR, Vedolin L.** Surgical management of neurological manifestations of mucopolysaccharidosis disorders. Mol Genet Metab. 2017;122S:41–48. DOI: 10.1016/j.ymgme.2017.09.011.
36. **Borlot F, Arantes PR, Quaio CR, Franco JF, Louren o CM, Bertola DR, Kim CA.** New insights in mucopolysaccharidosis type VI: neurological perspective. Brain Dev. 2014;36:585–592. DOI: 10.1016/j.braindev.2013.07.016.
37. **Charrow J, Alden TD, Breathnach CA, Frawley GP, Hendriksz CJ, Link B, Mackenzie WG, Manara R, Offiah AC, Solano ML, Theroux M.** Diagnostic evaluation, monitoring, and perioperative management of spinal cord compression in patients with Morquio syndrome. Mol Genet Metab. 2015;114:11–18. DOI: 10.1016/j.ymgme.2014.10.010.
38. **Solanki GA, Alden TD, Burton BK, Giugliani R, Horovitz DD, Jones SA, Lampe C, Martin KW, Ryan ME, Schaefer MK, Siddiqui A, White KK, Harmatz P.** A multinational, multidisciplinary consensus for the diagnosis and management of spinal cord compression among patients with mucopolysaccharidosis VI. Mol Genet Metab. 2012;107:15–24. DOI: 10.1016/j.ymgme.2012.07.018.
39. **Solanki GA, Sun PP, Martin KW, Hendriksz CJ, Lampe C, Guffon N, Hung A, Sisic Z, Shediac R, Harmatz PR.** Cervical cord compression in mucopolysaccharidosis VI (MPS VI): Findings from the MPS VI Clinical Surveillance Program (CSP). Mol Genet Metab. 2016;118:310–318. DOI: 10.1016/j.ymgme.2016.06.001.
40. **Bradley WG Jr, Scalzo D, Queralt J, Nitz WN, Atkinson DJ, Wong P.** Normal-pressure hydrocephalus: evaluation with cerebrospinal fluid flow measurements at MR imaging. Radiology. 1996;198:523–529. DOI: 10.1148/radiology.198.2.8596861.
41. **Kachur E, Del Maestro R.** Mucopolysaccharidoses and spinal cord compression: case report and review of the literature with implications of bone marrow transplantation. Neurosurg. 2000;47:223–229. DOI: 10.1097/00006123-200007000-00046.
42. **Lee C, Dineen TE, Brack M, Kirsch JE, Runge VM.** The mucopolysaccharidoses: characterization by cranial MR imaging. AJNR Am J Neuroradiol. 1993;14:1285–1292.
43. **Stoquart-Elsankari S, Lehmann P, Villette A, Czosnyka M, Meyer ME, Deramond H, Baledent O.** A phase-contrast MRI study of physiologic cerebral venous flow. J Cereb Blood Flow Metab. 2009;29:1208–1215. DOI: 10.1038/sj.jcbfm.jcbfm200929.
44. **Whitley CB, Belani KG, Chang PN, Summers CG, Blazar BR, Tsai MY, Latchaw RE, Ramsay NK, Kersey JH.** Long-term outcome of Hurler syndrome following bone marrow transplantation. Am J Med Genet. 1993;46:209–218. DOI: 10.1002/ajmg.1320460222.
45. **Buchinskaia NV, Kostik MM, Chikova IA, Isupova EA, Kalashnikova OV, Chasnyk VG, Gubin AV, Riabykh SO, Ochirova PV.** Skeletal manifestations for mucopolysaccharidoses of different types. Genij Orthopedii. 2014;(2):81–90. In Russian.
46. **Abelin Genevois K, Garin C, Solla F, Guffon N, Kohler R.** Surgical management of thoracolumbar kyphosis in mucopolysaccharidosis type 1 in a reference center. J Inherit Metab Dis. 2014;37:69–78. DOI: 10.1007/s10545-013-9630-2.
47. **Pauchard N, Garin C, Jouve JL, Lascombes P, Journeau P.** Perioperative medullary complications in spinal and extra-spinal surgery in mucopolysaccharidosis: a case series of three patients. JIMD Rep. 2014;16:95–99. DOI: 10.1007/8904_2014_325.
48. **Van der Linden MH, Kruyt MC, Sakkers RJ, de Koning TJ, Oner FC, Castelein RM.** Orthopaedic management of Hurler's disease after hematopoietic stem cell transplantation: a systematic review. J Inherit Metab Dis. 2011;34:657–669. DOI: 10.1007/s10545-011-9304-x.
49. **White KK.** Orthopaedic aspects of mucopolysaccharidoses. Rheumatology (Oxford). 2011;50 Suppl 5:v26–v33. DOI: 10.1093/rheumatology/ker393.
50. **Yasin MN, Sacho R, Oxborrow NJ, Wraith JE, Williamson JB, Siddique I.** Thoracolumbar kyphosis in treated mucopolysaccharidosis 1 (Hurler syndrome). Spine. 2014;39:381–387. DOI: 10.1097/BRS.0000000000000157.
51. **Korzh NA, Khmyzov SA, Korolkov AI, Ershov DV.** The method of temporary growth zone block in treating low extremity deformities in children (a review of literature review). Orthopaedics, traumatology and prosthetics. 2013;2:114–121. In Russian.
52. **Burghardt RD, Herzenberg JE.** Temporary hemiepiphysiodesis with the eight-Plate for angular deformities: mid-term results. J Orthop Sci. 2010;15:699–704. DOI: 10.1007/s00776-010-1514-9.
53. **Journeau P, Garin C, Polirsztok E, Jouve JL.** Bone dysplasia in mucopolysacchoridoses. Arch Pediatr. 2014;21 Suppl 1:S4–S13. DOI: 10.1016/S0929-693X(14)72253-5.
54. **Journeau P, Mayer J, Popkov D, De Gheldere, Lascombes P.** Epiphysiodese par plaque vissee extra-physaire pour la correction des deformations angulaires des membres inferieurs chez l'enfant et l'adolescent. In: Deformations des membres inf rieurs: De la consultation l'acte op ratoire (sous la direction P. Journeau, P. Lascombes). Sauramps M dical. Montpellier-Paris, 2009:49–55.
55. **O'heireamhoin S, Bayer T, Mulhall KJ.** Total hip arthroplasty in mucopolysaccharidosis type IH. Case Rep Orthop. 2011;2011:832439. DOI: 10.1155/2011/832439.
56. **Schroerlucke S, Bertrand S, Clapp J, Bundy J, Gregg FO.** Failure of Orthofix eight-Plate for the treatment of Blount disease. J Pediatr Orthop. 2009;29:57–60. DOI: 10.1097/BPO.0b013e3181919b54.
57. **Taylor C, Brady P, O'Meara A, Moore D, Dowling F, Fogarty E.** Mobility in Hurler syndrome. J Pediatr Orthop. 2008;28:163–168. DOI: 10.1097/BPO.0b013e3181649e25.
58. **Ransford AO, Crockard HA, Stevens JM, Modaghegh S.** Occipito-atlanto-axial fusion in Morquio-Brailsford syndrome. A ten-year experience. J Bone Joint Surg Br. 1996;78:307–313. DOI: 10.1302/0301-620x.78b2.0780307.
59. **Haddad FS, Jones DHA, Vellodi A, Kane N, Pitt MC.** Carpal tunnel syndrome in the mucopolysaccharidoses and mucolipidoses. J Bone Joint Surg Br. 1997;79:576–582. DOI: 10.1302/0301-620X.79B4.7547.
60. **Weisstein JS, Delgado E, Steinbach LS, Hart K, Packman S.** Musculoskeletal manifestations of Hurler syndrome: long-term follow-up after bone marrow transplantation. J Pediatr Orthop. 2004;24:97–101. DOI: 10.1097/00004694-200401000-00019.
61. **Garrido E, Tome-Bermejo F, Adams CI.** Combined spinal arthrodesis with instrumentation for the management of progressive thoracolumbar kyphosis in children with mucopolysaccharidosis. Eur Spine J. 2014;23:2751–2757. DOI: 10.1007/s00586-014-3186-1.
62. **Dede O, Thacker MM, Rogers KJ, Oto M, Belthur MV, Baratela W, Mackenzie WG.** Upper cervical fusion in children with Morquio syndrome: intermediate to long-term results. J Bone Joint Surg Am. 2013;95:1228–1234. DOI: 10.2106/JBJS.J.01135.
63. **Riabykh SO, Shusharina VL, Ochirova PV, Tret'iakova AN, Riabykh TV.** Perioperative risk reduction for vertebrologic surgeries in patients with hereditary diseases of the connective tissue. Genij Orthopedii. 2015;(4):48–52. In Russian. DOI: 10.18019/1028-4427-2015-4-48-52.
64. **Saifutdinov MS, Skripnikov AA, Ryabykh SO, Ochirova PV.** Score evaluation of intraoperative neurophysiological monitoring results of spinal deformity surgical correctionin genetically caused systemic skeletal pathology. Genij Orthopedii. 2017;23(2):201–205. In Russian. DOI: 10.18019/1028-4427-2017-23-2-201-205.
65. **Pavlova OM, Burtsev AV, Gubin AV, Ryabykh SO.** Posterior cervical screw fixation in children: the treatment experience. Hir. Pozvonoc. 2017;14(3):27–31. In Russian. DOI: http://dx.doi.org/10.14531/ss2017.4.27-31.
66. **Burtsev AV, Gubin AV, Ryabykh SO, Kotel'nikov AO, Pavlova OM.** Syndromic approach in assessing the surgical pathology of the cervical spine. Genij Orthopedii. 2018;24(2):216–220. In Russian. DOI: 10.18019/1028-4427-2018-24-2-216-220.

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Received 13.02.2019
Review completed 24.03.2019
Passed for printing 17.04.2019

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