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 pathology.


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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, heptosplenomegaly, 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).

Table 1

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>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</td>
</tr>
<tr>
<td>B</td>
<td>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</td>
</tr>
<tr>
<td>C</td>
<td>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</td>
</tr>
<tr>
<td>D</td>
<td>Case series report, or an uncontrolled study, or an expert opinion</td>
</tr>
</tbody>
</table>

RCT – randomized clinical trial.
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The vertebral syndrome in various types of mucopolysaccharidosis

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 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 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.

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**Table 2**

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

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

<table>
<thead>
<tr>
<th>Type of MPS/syndrome</th>
<th>Craniovertebral stenosis</th>
<th>Occipital-cervical instability</th>
<th>Thoracolumbar kyphosis</th>
<th>Scoliosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS I/Hurler</td>
<td>++*</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>MPS I/Hurler-Scheie, Scheie</td>
<td>++</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MPS II/Hunter</td>
<td>++</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MPS IV/Morquio</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>MPS VI/Maroto-Lamy</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

* 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]

<table>
<thead>
<tr>
<th>Objective</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement of neurological condition*</td>
<td>Anticholinesterase drugs, anticonvulsants, dehydration. Currently, there is no effective treatment of neurological complications</td>
</tr>
<tr>
<td>Improvement of orthopedic status</td>
<td>Corset therapy, massage, exercise therapy, orthotics, orthopedic correction of pathological arrangements, contractures, etc.</td>
</tr>
<tr>
<td>Social adaptation**</td>
<td>Physical and functional rehabilitation, training to use assistive devices — verticalizers, braces, devices</td>
</tr>
</tbody>
</table>

* 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]

<table>
<thead>
<tr>
<th>Examination</th>
<th>Examination rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination by a neurologist and an orthopedist</td>
<td>6 months</td>
</tr>
<tr>
<td>X-ray of the cervical spine (upright and lateral projections, flexion, extension)</td>
<td>2 to 3 years</td>
</tr>
<tr>
<td>X-ray of the thoracic and lumbar spine with involvement of the hip joints (upon progression)</td>
<td>2 to 3 years (every 6 months)</td>
</tr>
<tr>
<td>MRI of the cerebral and spinal conductive pathways (tractography, if possible)</td>
<td>1 year</td>
</tr>
<tr>
<td>Functional MRI of the cervical spine with flexion and extension</td>
<td>1–3 years</td>
</tr>
<tr>
<td>CT of the craniovertebral junction + cervical + thoracic + lumbar spine + CT of the upper respiratory tract and lungs</td>
<td>Before surgery</td>
</tr>
</tbody>
</table>
Table 6
The system for assessment of spinal cord compression at the craniovertebral junction level to decide the need for surgical treatment [35]

<table>
<thead>
<tr>
<th>Score</th>
<th>Clinical neurological examination</th>
<th>Test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>— normal neurological findings;</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>— increased/decreased tendon reflexes, lateral differences in muscle reflexes;</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>— pyramidal tract signs: Babinski reflex, Gordon reflex, Oppenheim reflex, muscle twitching;</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>— paresis or weakness of the upper and/or lower limbs</td>
<td></td>
</tr>
</tbody>
</table>

Somatosensory evoked potentials of the median nerve

<table>
<thead>
<tr>
<th>Score</th>
<th>Test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>— normal;</td>
</tr>
<tr>
<td>1</td>
<td>— prolongation of at least one of the interpeak latencies: N9/P13, N9/N13b, or N13a/N20 (&gt; 2.5 SD)*;</td>
</tr>
<tr>
<td>2</td>
<td>— lack of P13 and/or N13b (subcortical);</td>
</tr>
<tr>
<td>3</td>
<td>— lack of N20 (cortical)</td>
</tr>
</tbody>
</table>

MRI

<table>
<thead>
<tr>
<th>Score</th>
<th>Test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>— no spinal cord compression;</td>
</tr>
<tr>
<td>1</td>
<td>— spinal cord compression (no CSF in any direction);</td>
</tr>
<tr>
<td>3</td>
<td>— myelomalacia signs</td>
</tr>
</tbody>
</table>


Table 7
Basic principles of surgical treatment of spinal pathology associated with different types of mucopolysaccharidosis [40–50]

<table>
<thead>
<tr>
<th>Surgical treatment principles</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decompression and stabilization</td>
<td>Stenosis, instability, and stenosis combined with instability at the craniovertebral junction level, mechanical neurological instability</td>
</tr>
<tr>
<td>Deformity correction with instrumented stabilization of the spine</td>
<td>Progression of spinal deformity, worsening of somatic and neurological statuses</td>
</tr>
</tbody>
</table>

Table 8
Surgical treatment approach for spinal pathology in mucopolysaccharidosis [22, 46–47, 50, 61–62]

<table>
<thead>
<tr>
<th>Spine region</th>
<th>Deformity correction</th>
<th>Spinal cord decompression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>+/−</td>
<td>+</td>
</tr>
<tr>
<td>Thoracic</td>
<td>+</td>
<td>+/−</td>
</tr>
<tr>
<td>Lumbar</td>
<td>+</td>
<td>−</td>
</tr>
</tbody>
</table>
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Surgical treatment approach for spinal pathology in patients with different types of mucopolysaccharidosis [63–66]: RF – respiratory function; IONM – intraoperative neuromonitoring.

Assessment of the syndromic status and risk of surgical treatment

Discussion of the step-by-step protocol of surgery with assessment of the patient’s functional state (ECG, blood pressure, saturation, RF, blood loss volume) and spinal cord (dynamics of spontaneous somatosensory and motor evoked potentials based on IONM data)

Assessment of the syndromic status and risk of surgical treatment

Discussion of the step-by-step protocol of surgery with assessment of the patient’s functional state (ECG, blood pressure, saturation, RF, blood loss volume) and spinal cord (dynamics of spontaneous somatosensory and motor evoked potentials based on IONM data)

- possibility of completion at each step;
- coordinated actions of a multidisciplinary team

Monitoring of indicators at all surgical stages: after intubation, during turning and positioning, decompression, correction, fixation (depending on surgery type), and extubation

Features of the anesthetic protocol and intensive care:
- IONM before turning after intubation;
- difficulty of positioning with head fixation (Mayfield frame, halo);
- readiness for complex intubation using fiber optics and a video laryngoscope;
- ultrasound monitoring for central venous catheterization;
- postoperative follow-up in the intensive care unit

Fig. 1

Assessment of the syndromic status and risk of surgical treatment

Discussion of the step-by-step protocol of surgery with assessment of the patient’s functional state (ECG, blood pressure, saturation, RF, blood loss volume) and spinal cord (dynamics of spontaneous somatosensory and motor evoked potentials based on IONM data)

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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
Invitation for discussion

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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

Table 9
Variants of surgical correction for spinal pathology with allowance for vertebral syndrome features

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

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


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