

New recommendations for the care of patients with mucopolysaccharidosis type I

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ABSTRACT

Considering the advances made on mucopolysaccharidosis type I after the consensus study published by a group of experts in Argentina in 2008, recommendations about genetic testing, cardiological follow-up, airway care, hearing impairment detection, spinal and neurological conditions, as well as current treatments, were reviewed. Emphasis was placed on the need for early diagnosis and treatment, as well as an interdisciplinary follow-up.

Key words: mucopolysaccharidosis type I, classification, treatment, diagnosis, follow-up.

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INTRODUCTION

In 2008, a consensus study was published about the diagnosis and treatment of mucopolysaccharidosis type I (MPS I) in Argentina.¹ Time elapsed regarding the treatment and follow-up in our setting and in the world underscores the need to review the recommendations about some aspects of the disease.

Clinical forms

MPS I patients were classified according to the degree of severity into three clinical forms: Hurler, Hurler-Scheie, and Scheie. At present, this disease has been classified into severe form (SF), formerly called Hurler syndrome, and attenuated form (AF), which comprises the Hurler-Scheie and Scheie syndromes.¹

Genetics

MPS I is an autosomal recessive disease whose genetic heterogeneity partly accounts for its clinical heterogeneity. The responsible gene is *IDUA*, which contains 14 exons and is localized on the 4p16.3 chromosomal locus. Today, close to 100 mutations are known, and 20 of them are involved in 85 % to 90 % of cases.

In 90 % to 95 % of the cases, the mutations are identified by complete sequencing, since it is not possible to identify them using simpler techniques. There are missense (AF), nonsense (SF), and deletion mutations.

In the SFs, the most frequent mutations are W402X (45 %) and Q70X (16 %), both in homozygosity. In the AFs, heterozygous variants combined with one of them may be found.

The clinical form cannot be determined by enzyme assays or biochemical markers. The genotype-phenotype correlation may be especially helpful in newborn infants.

Out of 538 MPS I cases in the international registry, 67.6 % of the 380 SFs had mutations that allowed predicting the phenotype.² Every diagnosed patient should receive genetic counseling.

Cardiovascular assessment

Between 88 % to 93 % of the patients with SFs and AFs have cardiac manifestations^{3,4} (Table 1). Available treatments prolong survival, but coronary heart disease and valve

diseases occur despite treatment^{5,6} causing a high morbidity and mortality. Fifty percent of patients with the SF die because of a cardiac cause.⁷⁻⁹

Valve abnormalities were reported in 35 % of Latin American patients with the SF and 54 % with the AF, versus 73 % and 87 % in the rest of the world. This difference might be related to a regional phenotype or to the way the diagnostic assessment is performed.¹⁰

The following is recommended for cardiological diagnosis and management:

- Cardiovascular examination, electrocardiogram (for abnormal heart rhythm) and baseline echocardiograms.
- In the follow-up:¹¹⁻¹³ Echocardiogram every 1 to 2 years if there are no abnormalities or if these are mild. Every 6 months or more frequently when there are moderate to severe conditions.

- Holter monitoring, only indicated for palpitations or ECG picked-up arrhythmias.
- Cardiopulmonary exercise testing; difficult to perform due to skeletal abnormalities; no studies support its use.
- For suspected coronary artery disease, multislice computed tomography, myocardial perfusion, and CT angiogram or MR angiography are performed when the disease of great vessels is suspected.
- In the future, it will be necessary to determine the vascular risk, calculating the vascular age with a Doppler echocardiogram of the neck vessels and the pulse wave velocity.¹¹

Airway assessment

Large airway obstruction is a serious problem.¹⁴ The hypertrophy of palatine tonsils and adenoids results in snoring, obstruction, and

TABLE 1. Most important cardiac manifestations

Cardiac condition	Frequency	Manifestation	Diagnosis and follow-up	Modifications with treatment
Mitral/aortic valve disease	Mitral valve disease is more frequent.	Regurgitation and stenosis.	Echocardiogram (57 % has normal auscultation). Concerning patients with attenuated forms, 14 % would require valve replacement.	HSCT and ERT neither modify nor stop progression.
Myocardial involvement	Very frequent in severe forms.	Hypertrophy (83 %). Dilated cardiomyopathy. Diastolic dysfunction in 50 %.	Echocardiogram. Electrocardiogram: hypertrophy is not shown due to the low conductivity of glycosaminoglycans.	HSCT and ERT improve hypertrophy and ventricular function.
Coronary involvement	Less frequent than in other mucopolysaccharidosis.	Diffuse compromise with ischemia leading to a dilated cardiomyopathy.	Multislice CT and myocardial perfusion for the diagnosis. Electrocardiogram: no evidence of ischemia.	The effect of the HSCT and ERT on the coronary lesion will depend on the previous severity of this condition. Other publications state that this does not have an influence.
Arterial involvement	Dilation of the aortic root in 38 % of the severe forms. Arterial hypertension in 32 % of patients.	Attenuated types of stenosis. Lower limb pain and claudication. HTN: involvement of the renal arteries.	BP monitoring. Clinical suspicion. Echocardiogram and arterial Doppler ultrasound.	No data available.
Pulmonary hypertension	Rare.	Dyspnea. High morbidity and mortality.	Echocardiogram.	No data available.
Endothelial dysfunction	Increased risk in MPS I.	In adolescents and pre-adolescents, vascular age is equivalent to that of a 40-year-old individual.	Neck-vessel Doppler ultrasound.	Decreases with ERT and HSCT although endothelial function is not recovered.

HSCT: hematopoietic stem cell transplantation; ERT: enzyme replacement therapy; HTN: arterial hypertension; BP: blood pressure; MPS I: mucopolysaccharidosis type I.

obstructive sleep apneas. They should be studied with sleep polysomnography and lateral neck X-ray in sniffing position.^{15,16}

Tonsillectomy and adenoidectomy improve ventilation and the deleterious effect of nocturnal hypoxia on the central nervous system (CNS) and other organs. It should be done carefully because of possible cardiac complications, added to the presence of subglottic infiltrates.¹⁷

With increasing age, scoliosis and thoracic stiffness develop, together with restrictive ventilatory impairment. Glycosaminoglycan accumulation on the tracheal and bronchial walls worsens the obstructive ventilatory impairment, so a tracheostomy may be required.¹⁸ Lung interstitial infiltration in the newborn infant has been described.¹⁹ Difficult airways should be evaluated before surgery, as a tracheostomy can prevent post-operative complications.^{20,21}

Audiological evaluation

Recurrent diseases of the middle ear are frequent and early. Repeated abnormal hearing screening tests might lead to the suspicion of mucopolysaccharidosis. If there is progressive hearing loss, it should be re-assessed at 6, 9, and 12 months.

Hearing loss is of conductive or mixed type and some cases progress to neurosensory type. Glycosaminoglycan deposits occur first in the tympanic membrane, then in the inner ear, and finally at a central level.

When there is a moderate to severe conductive hearing impairment, the ear canal must be stimulated to preserve the quality of communication. Severe conduction impairment no longer has an indication for treatment.

The indication for hearing aids, cochlear and osseointegrated implant processors depends on the patient's hearing level and overall commitment. An audiological evaluation should include subjective or behavioral tests for the diagnostic confirmation.²²

Spinal health

An anterior and medial defect of the vertebral body, the classic platyspondyly aspect with the presence of an anterior peak or notch, because of an incomplete endochondral ossification of the vertebral body,^{23,24} trapezoid- or wedged-shaped vertebrae,²³ large intervertebral discs in relation to the hypoplastic vertebrae, the presence of a posterior intracanal bulging,^{26,27} and spinal canal stenosis at different levels are observed. Cervical

pathology is less frequent in type I than in types IV and VI. Hypoplasia of the odontoid process,²⁵ in some cases, associated with atlantoaxial cervical instability, is detected in the cervical radiographic pair, in maximum flexion and extension.

Progressive kyphoscoliosis leads to decompensation of the trunk, instability, and potential neurological compromise.^{28,29} Patients range from being asymptomatic to presenting neurological involvement secondary to spinal cord compression.^{30,31}

Out of the 42 operated patients (assisted at Hospital Garrahan) with mucopolysaccharidosis of different types (IV, VI, and I), 55 % had neurological involvement. Twenty five percent had odontoid hypoplasia; 21 %, atlantoaxial instability; and 21 %, narrowing of the cervical spinal canal due to glycosaminoglycan deposits.

If cervical stenosis is suspected at the time of the clinical examination, radiographic studies, static magnetic resonance and preoperative CT scans should be performed. A specialized assessment is required.³² Somatosensory and motor evoked potentials, sometimes urodynamic testing and polysomnographic evaluations are also performed.

Surgery is performed by releasing compressions and preserving the neurological structures, using subsequent decompression techniques, mostly associated with arthrodesis.³² Prophylactic versus therapeutic fusions are controversial. Surgery should be done at an early stage when indicated.³³

The most frequent deformity is kyphosis with apex at the L1 or L2 region, followed by scoliosis, or combined. In children under 7 years of age with kyphoscoliosis and curves with an angle of less than 50 degrees, a custom-made thermoplastic thoracolumbosacral orthosis is used, 22 hours per day, which allows practising physical activity or sports if there is no spinal risk at the cervical or thoracolumbar level. For older ages, with curves between 50 and 70 degrees or more, instrumental fusions are indicated at a later stage. With a deformity associated with spinal stenosis and neurological deficit, a double approach is used (anterior decompression and arthrodesis + posterior instrumental fusion). The surgical team includes highly qualified anesthesiologist and neurophysiologist.

Neurological manifestations

MPS I has a progressive involvement of the central (CNS) and peripheral nervous systems (PNS), which varies according to the clinical form.

They include cognitive impairment, behavioral problems, sleep disorders, hydrocephalus and spinal cord compression; root, peripheral nerve and cranial nerve entrapment.

Cognitive impairment

In the SF, after a period of normal development, a stagnation occurs between the first and second year of life, followed by a fast cognitive deterioration.³⁴⁻³⁶ Approximately 20 intellectual quotient (IQ) points are lost per year.³⁷ Neurodegeneration involves heparan sulfate deposit, which acts as a matrix of neuroinflammation and overexpression of gangliosides with a neurotoxic effect, which induces ectopic dendritogenesis and abnormal synaptogenesis.³⁸

The AFs are not entirely free of cognitive developmental problems. For every year that treatment is delayed, there will be 9 IQ points less.³⁹ Some mutations (L238Q) favor late psychiatric manifestations, such as self-isolation and depression.⁴⁰

There are no biomarkers to determine the presence of neurodegeneration. This is measured by formal cognitive assessment over time. Up to age 3, it is recommended to use the Bayley-III scale, which provides age-equivalent scores. For those over 3 years old, IQ can be measured with the Wechsler scales. For the adaptive behavior, the Vineland scale is recommended for all ages.³⁴

Early hearing impairment can, *per se*, affect language. New functional neuroimaging and their correlation with higher mental functions are still being studied.⁴¹ For a better long-term cognitive prognosis in the SFs, early transplantation should be indicated.⁴²

Hydrocephalus

Hydrocephalus is a relatively frequent complication in mucopolysaccharidoses, especially in MPS I and II, and, together with glycosaminoglycan deposits in the different planes, it contributes to macrocephalus. It presents with slow neurological disorders, progressive deterioration, and rarely, papilledema, headache, and vomiting.

From 80 % to 85 % of cases are communicating.⁴³ The dynamics of cerebrospinal fluid (CSF) circulation is altered by glycosaminoglycan deposit with obstruction of the subarachnoid spaces and Pacchionian granulations, with reduction of the venous drainage.

In children, it is corrected when required, with ventriculoperitoneal, ventriculoatrial or lumboperitoneal shunts to shorten the subcutaneous path. The accumulation of glycosaminoglycans can predispose to blockage of the shunt.

Glycosaminoglycan deposits in the white matter and basal ganglia promotes tissue destruction, compression of the parenchymal vessels, dilation of the perivascular and subarachnoid spaces, which leads to cerebral atrophy with passive dilation of the ventricles and mimics hydrocephalus. This one does not require treatment.

Spinal cord compression

Glycosaminoglycan deposits in the dura mater and ligaments causes spinal cord compression and myelopathy. Early detection and surgical correction prevents irreversible damage of the spinal cord. Initial, mild, insidious signs (progressive weakness, clumsiness, fatigue, hyperreflexia, pain, and paresthesias) may be confused with signs of osteoarticular diseases.^{37,38}

Diagnosis

It is performed by showing in the patient with suggestive signs and symptoms, the deficiency of the enzyme alpha-L-iduronidase in purified leukocytes or blood drops on filter paper. Newborn screening can also be performed.^{1,8,9}

The methods available today make it unnecessary to measure enzyme activity in fibroblast culture. *Table 2* shows the advantages and limitations of the available biochemical methods. The molecular study is not essential for diagnosis, but it is necessary to indicate the treatment.

Available treatments

The specific treatments are allogeneic hematopoietic stem cell transplantation (HSCT) or enzyme replacement therapy (ERT). The European consensus forwards the treatment decision-making to a team of experts, which is an excellent recommendation to be applied in our setting.⁴⁴

HSCT is the treatment of choice for the SF to replace the defective monocytic-macrophage system with that of the donor, which secretes the missing enzyme. Offered at < 2 years and with an IQ > 70, it can stop progressive neurocognitive deterioration and damage to other organs.^{8,44} Those older than 2 years and with IQ < 70 have poor benefit from HSCT.

Age is the most important outcome measure. By transplanting before 12 months of age, the best cognitive prognosis is achieved and, before 9 months, the neurocognitive development achieved may be normal.^{42,45-48}

Since the first HSCT performed in 1981 to date, more than 500 patients have been transplanted. In Argentina, between 2009 and 2018, 17 patients underwent 20 HSCT* (* data provided by the National Institute for Organ and Tissue Procurement for Transplantation [Instituto Nacional Central Único Coordinador de Ablación e Implante, INCUCAI]).

About 25 % will have a related donor; the rest will require an international registry search.

There may be a graft loss of up to 30 %, but busulfan-based myeloablative conditioning has improved this figure. With the busulfan/fludarabine regimen, survivals > 90 % have been reported.^{42,44,45,49}

Five-year overall survival (OS) rate ranges from 74 % to 95 %, and event-free survival from 63 % to 90 %, depending on the type of donor and the sources of hematopoietic stem cells used for the transplantation.^{46,47} Transplant-related

TABLE 2. Diagnostic methods

Type of sample	Advantages	Limitations
Glycosaminoglycans in urine		
Quantitative Glycosaminoglycan concentration in urine measured and corrected to urinary creatinine levels.	<ul style="list-style-type: none"> • 24-hour urine test • It is useful as a screening method for those mucopolysaccharidoses with high glycosaminoglycan levels in urine. • The test can be used to monitor the course of the disease or the response to treatment. 	<ul style="list-style-type: none"> • Non-specific for heparan and dermatan sulfate. • Some patients may excrete normal or slightly increased amounts of glycosaminoglycans. • Cut-off levels should be set according to the patient's age. Glycosaminoglycan concentration decreases as the patient's age increases. • Results can be false positive if urine has a high creatinine level or negative if urine is very diluted. • The sample is difficult to obtain in patients who do not have sphincter control (young children or those with mental retardation). • Sample delivery to a referral center. • A negative test may result in a patient not being studied further.
Qualitative It specifically identifies the type of glycosaminoglycans present in the urine, which allows classifying the type of mucopolysaccharidosis the patient may have.	<ul style="list-style-type: none"> • 24-hour urine test • A specific pattern of excretion can be observed or different mucopolysaccharidoses even in cases where glycosaminoglycan quantification was normal. 	<ul style="list-style-type: none"> • The profile obtained does not allow to tell the difference between MPS I and II. • The sample is difficult to obtain in patients who do not have sphincter control (young children or those with mental retardation). • A specialized laboratory is required to perform this assay.
Alpha-L-iduronidase enzyme activity assay		
Leukocytes	<ul style="list-style-type: none"> • 10 mL of heparinized blood. • Highly sensitive and specific method. • Once the sample is conditioned, it can be stored for a long time. 	<ul style="list-style-type: none"> • The sample must be delivered at the laboratory within 24 hours of being obtained. • The required sample volume is high, especially in pediatric patients. • A specialized laboratory is required to perform this assay.
Fibroblasts	<ul style="list-style-type: none"> • Skin biopsy. • Multiple assays can be performed in the same specimen. • Once the sample is conditioned, it can be stored for a long time. 	<ul style="list-style-type: none"> • Invasive specimen collection method. • The development of the fibroblast culture requires weeks to be able to do the enzyme assay, which delays the result. • Transportation might affect the sample. • A specialized laboratory is required to perform this assay.
BDFP	<ul style="list-style-type: none"> • Filter paper soaked in whole blood (the same that is used for newborn screening). • Minimally-invasive sample collection. • Easy transportation. • Multiple assays can be performed in the same specimen. • Allows for large-scale testing. • Good correlation of results obtained in leukocytes. 	<ul style="list-style-type: none"> • A specialized laboratory is required to perform this assay. • Results obtained should be confirmed in leukocytes or by genetic testing.

BDFP: blood drop on filter paper.

mortality ranges from 10 % to 25 %, mainly due to viral infectious causes, graft versus host disease (GVHD), pulmonary complications, bleeding, and multiple organ failure.^{46,49}

Cord blood (CB) stem cells have been shown to be more likely to achieve donor chimerism ($p = 0.39$) and normal enzyme levels ($p = 0.07$) (92 % and 98 %, respectively) compared to other sources. OS with CB (identity 6/6), of 81 %, is comparable to the related identical donor transplantation. It would be a preferential source because of the rapid availability and larger population of primitive hematopoietic stem cells. The period of aplasia is longer, with the consequent higher risk of viral reactivations, and only one donation per donor is feasible. Results obtained with CB (OS ~90 %) are better than those obtained with bone marrow or peripheral blood stem cells. They could be influenced by supportive care, conditioning, and high degree of compatibility since they are from the last decade.^{45-47,49}

Options for a HSCT would be as follows:

1. Related identical donor (sibling, with molecular studies).
2. Unrelated donor (URD) 10/10 or CB 6/6 (high-resolution human leukocyte antigen, HLA).

Enzyme activity reaches values comparable to those of the donor in the first 3 months. Approximately 50 % of the normal value is achieved with a carrier donor and 100 % with an unaffected donor.⁴⁹

Compromise of some organs might persist depending on the previous disease burden. Hepatosplenomegaly, ventilatory symptoms, and myocardial hypertrophy improve, although valve alterations may persist. Corneal opacity improves, but retinal degeneration may occur. Hearing also improves, even though a neurosensorial component may be present.

Short stature will remain. Skeletal dysplasia persists. It improves odontoid dysplasia and cervical stability, joint mobility of the upper limbs, more than that of the lower limbs. There may be delayed puberty and reduced fertility.^{42,43,46} Cognitive impairment improves 6-12 months after transplantation because it requires the presence of donor macrophages transporting microglial enzymes and the replacement turnover rate is slow.^{42,45,49,50}

Long-term prognosis of a HSCT depends on age, baseline clinical status, and complete chimerism. Early diagnosis, timely referral, and

rapid admission to experienced transplant centers are critical.^{42,45,49,50} Follow-up should be done by a multidisciplinary and interdisciplinary team, with active participation of the transplant team during, at least, 1 year.

ERT with recombinant human laronidase is for AFs, not for SFs, because it does not cross the blood-brain barrier (BBB).⁴⁵ The best treatment outcome depends on age, severity, and each patient's degree and type of clinical compromise.⁴⁵

With a HSCT, compared to an ERT, a better metabolic control is obtained.⁵¹ It does not improve CNS, bone, heart valves or corneal conditions. Pre-transplant ERT improves respiratory function and cardiomyopathy. It does not increase the risk for developing immune-mediated reactions nor it negatively affects the graft nor promotes GVHD. An improvement of cognitive functions was reported in relation to post-transplant ERT, probably because of the improvement of the other clinical manifestations.⁵²

ERT modifies the natural history of the disease in the AFs, improves hepatosplenomegaly, skin thickness, respiratory function, and cardiomyopathy, but does not reverse the abnormal range of the already established joint mobility problems and conditions, such as dysostosis, valve disease, and corneal opacity. Early ERT in the AFs, before the establishment of the inflammatory cascade after the glycosaminoglycan deposit, prevents the occurrence of some of these manifestations. The indication differs, then, from the criteria established in 2008 to treat the AFs.¹ The sooner it starts, the better.

A better course was reported with the 12 year follow-up of a patient who was administered ERT at 5 months old, compared to his sister who started treatment at 5 years old. The younger brother maintained normal facies and fewer skeletal, joint, and myocardial lesions; he was in the 97th percentile, and his sister in the 10th percentile, and reached an IQ of 100, while his sister reached 70.⁵³ ERT benefit appears minimal in non-transplanted patients with SFs.⁵⁴ It is suggested that a group of experts should evaluate this indication on an individual basis.⁵⁵

CONCLUSIONS

Early diagnosis and treatment modify the course of the disease. Ideally, an interdisciplinary team should be in charge of the follow-up. ■

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