



## Mucopolysaccharidoses: From understanding to treatment, a century of discoveries

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### Abstract

After the first description of a patient recognized as a MPS case was made in 1917, several similar cases were described and identified. Observations reported in the middle of the twentieth century concerning the presence of acid mucopolysaccharides (later called glycosaminoglycans, or GAGs) in tissues and especially in urine of patients were instrumental in providing an identity for these diseases, which became referred as “mucopolysaccharidoses” (MPS). In the late 1960's it was demonstrated that MPS were caused by defects in the breakdown of GAGs, and the specific enzyme deficiencies for the 11 types and subtypes of MPS were identified thereafter. Genes involved in the MPS were subsequently identified, and a large number of disease-causing mutations were identified in each one. Although individually rare, MPS are relatively frequent as a group, with an overall incidence estimated as 1:22,000. The increased excretion of urinary GAGs observed in the vast majority of MPS patients provides a simple screening method, the diagnosis usually being confirmed by the identification of the specific enzyme deficiency. Molecular analysis also plays a role, being helpful for phenotype prediction, prenatal diagnosis and especially for the identification of carriers. As the diseases are rare and diagnosis requires sophisticated methods, the establishment of reference laboratories for MPS identification is recommended. The successful experience of the MPS Brazil Network in providing access to information and diagnosis may be considered as an option for developing countries. The development of therapeutic strategies for MPS, including bone marrow/hematopoietic stem cell transplantation (BMT/HSCT) and enzyme replacement therapy (ERT), changed the natural history of many MPS types. However, some challenges still remain, including the prevention of cognitive decline which occurs in some MPS. Newer approaches, such as intratechal ERT, substrate reduction therapy, read-through, gene therapy and encapsulated modified cells may provide a better outcome for these diseases in the near future. As early diagnosis and early treatment seems to improve treatment outcomes, and as newborn screening is now technically feasible, pilot programs (including one in progress in an area with high-incidence of MPS VI in northeastern Brazil) should provide information about its potential impact in reducing the morbidity associated with MPS diseases.

*Keywords:* mucopolysaccharidoses, lysosomal diseases, enzyme replacement therapy, prenatal diagnosis, newborn screening.

### The Clinical Identity

Many likely cases of mucopolysaccharidosis (MPS) were probably observed in the past, before the first description of patients recognized as MPS cases was made by Dr. Charles Hunter in 1917 (Hunter, 1917). He described two Canadian sibs, both boys, affected by a similar disease, characterized by coarse facies, large abdomen, bone dysplasia and certain other signs and symptoms. Two years

later, Dr. Gertrud Hurler, a German pediatrician, reported two unrelated boys with a similar picture (Hurler, 1919). She described very well the visceromegaly and bone abnormalities present in the patients.

Many similar cases were described during the following years, and the term “gargoylism” was used for some time, as it was thought that the large neck and coarse facies of the patients resembled the images of the medieval cathedral gargoyles. As observed with the patients described by Hunter and Hurler, most cases were reported with family recurrence, but in some families only boys were affected, suggesting the occurrence of an x-linked form in these cases.

In 1929, the Uruguayan pediatrician Luis Morquio described a form of “familial skeletal dystrophy” affecting four of five children born to consanguineous parents from Swedish descent. This report (Morquio, 1929), along with another publication on similar cases made in the same year by the radiologist Brailsford (1929), led to the recognition of a new form of skeletal dysplasia, with no visceromegaly or cognitive impairment, later identified as Morquio syndrome (at this time, no relationship with the cases described by Hunter and Hurler was recognized).

Many years later, American ophthalmologists described an attenuated form of this syndrome, based on the corneal opacity observed in an adult patient (Scheie *et al.*, 1962). This condition was first referred to as Scheie syndrome, but later was incorporated within the Hurler syndrome spectrum.

Subsequently, Sanfilippo *et al.* (1963) described in the United States a form of mental retardation associated with mucopolysacchariduria, but with less pronounced visceral and skeletal manifestations than reported in previously-described MPS patients. This form was designated Sanfilippo syndrome. In the same year, Maroteaux *et al.* (1963) described in France a new form of dysostosis with mucopolysacchariduria, but without cognitive impairment, which became known as Maroteaux-Lamy syndrome.

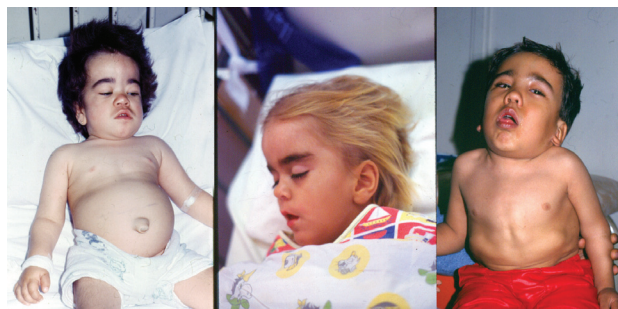
Sly and colleagues reported in 1973 an American boy with skeletal changes consistent with a mucopolysaccharidosis, hepatosplenomegaly, and granular inclusions in granulocytes. He had hernias, unusual facies, protruding sternum, thoracolumbar gibbus, vertebral deformities, and mental deficiency (Sly *et al.*, 1973). This condition became known as Sly syndrome. It is noteworthy that although this first reported case of MPS VII was in a child, many of the subsequent cases were presented *in utero* as hydrops fetalis.

In the nineties, Natowicz *et al.* (1996) described in the United States the clinical and biochemical manifestations of hyaluronidase deficiency, a very rare type of MPS. Further cases of hyaluronidase deficiency were described more recently, suggesting that this type of MPS may be more frequent than initially thought (Imundo *et al.*, 2011).

After the diseases were fully identified in terms of their biochemical and molecular bases, it became clear that a large clinical variability is present within each MPS type, with severe and attenuated forms and a large spectrum of clinical presentation ranging from the most severe to mildest forms. Figure 1 illustrates the clinical heterogeneity present in MPS diseases. Although the rate of progression is different from patient to patient, in all patients the disease is progressive and ultimately fatal, making these conditions a challenge for the families, doctors and health care systems.

### The Chemical Identity

Even though the early clinical descriptions of Hunter and Hurler suggested that storage was present in the cases



**Figure 1** - Three distinct phenotypes in MPS diseases: left - MPS I patient showing visceromegaly and cognitive decline; center - MPS III B patient showing mental deterioration without major somatic findings; right - MPS IV A patient showing skeletal dysplasia without coarse facies and visceromegaly and with normal intelligence.

reported, the nature of this storage material was only confirmed in the mid-twentieth century. Observations on the presence of acid mucopolysaccharides (later called glycosaminoglycans, or GAGs) in tissues (Brante, 1952; Costales and Garcia-Palacio, 1956) and urine (Dorfman and Lorincz, 1957; Meyer *et al.* 1958) of affected patients were instrumental in providing an identity for this group of diseases, which became referred to as “mucopolysaccharidoses”.

In addition to the increased excretion of GAGs in urine, the study on the relative amounts of the different GAG species (Teller *et al.*, 1962) provided a basis for attempts to classify the different diseases in this group.

### Summing up the Information - A Classification

Victor McKusick, who was very active in collecting observations on heritable connective tissue disorders and in linking such observations with the concept of inborn errors of metabolism proposed by Garrod, made the first attempt to classify the mucopolysaccharidoses, considering the clinical, genetic and biochemical information available (McKusick, 1969). In his classification, six different entities were included (the Hurler, Hunter, Sanfilippo, Morquio, Scheie and Maroteaux-Lamy syndromes), based mainly on the clinical characteristics and chemical composition of urinary GAGs. Although the Hunter syndrome overlaps considerably with the Hurler syndrome in terms of clinical and biochemical aspects, it was considered a distinct entity because the mechanism of inheritance was X-linked recessive, while the Hurler syndrome and all the other MPS were inherited as autosomal recessive traits.

### The Understanding of the Basic Defect

Although it was then known that abnormal amounts of GAGs were accumulated in MPS patients, the demonstration that the problem was in the degradation pathway was confirmed only in 1968 by the group of Elisabeth Neufeld (Fratantoni *et al.*, 1968a). Shortly thereafter this group also provided a major contribution to the understand-

ing of the basic defect underlying MPS by performing informative cell complementation studies. When co-cultivating cells from patients with different MPS types, the occurrence of cross-correction was observed when such cells were from patients with MPS I and MPS II (Fratantoni *et al.*, 1968b), and also in all mixes of MPS types, except when cells from patients with MPS I (Hurler) and MPS V (Scheie) were mixed. The conclusion was that patients with MPS I and MPS V, who were identified as belonging to the same cell complementation group, had the same basic defect. These experiments, in showing the uptake of correcting factors by deficient cells, provided also a rationale for therapies, such as bone marrow transplantation and enzyme replacement therapy.

The decade of the 1970s was marked by the search for specific enzyme deficiencies present in the different MPS types. Each of these enzymes was normally involved with a different step in the degradation of a particular GAG within the lysosomes of cells, and the MPS diseases were thus recognized as examples of lysosomal storage diseases. These enzyme studies confirmed that MPS I and MPS V are the severe and the attenuated ends of the spectrum of the same disease (MPS I,  $\alpha$ -iduronidase deficiency) (Bach *et al.*, 1972), that the MPS III phenotype could be caused by four different enzyme defects, and MPS IV by two different enzyme defects. A consequence of the identification of specific enzyme deficiencies was that the classification of MPS was completely modified (Table 1).

## Molecular Genetics of MPS

Following enzyme identification, the next cycle of discoveries on MPS, had its focus on the identification of disease causing genes. This started in 1987 with the identification of the gene implicated in MPS VII (Oshima *et al.*,

1987) and was completed only in 2006 with the identification of the gene for MPS III C (Fan *et al.*, 2006). The MPS are largely heterogeneous regarding gene defects, with deletions, rearrangements and a large number of different mutations found in each MPS type. A genotype-phenotype relationship is generally observed, with a trend for missense mutations leading to less severe manifestations when compared to nonsense mutations and large gene rearrangements, but prediction of the clinical course from molecular findings is sometimes difficult to make on the individual basis.

## Epidemiology

MPS are rare diseases, with data on the incidence of individual types available for only a few countries and regions. The overall incidence is estimated as 1 in 22,000 individuals considering all MPS types (Meikle *et al.*, 1999; Poorthuis *et al.*, 1999). The fact that MPS are clinically very heterogeneous leads us to infer that the frequency of these diseases should be higher than presently estimated, as many more attenuated cases may remain undiagnosed. The results of pilot screening programs for another lysosomal storage disease (Fabry disease) seem to confirm this prediction (Spada *et al.*, 2006; Hwu *et al.*, 2009; Lin *et al.*, 2009). The relative frequency of each MPS type in Brazil indicates that MPS II is the most frequent one, followed by MPS I and MPS VI (unpublished data from the MPS Brazil Network).

## A Guide to the Diagnosis of MPS

The recognition that almost all MPS patients present mucopolysacchariduria, which may be easily identified by qualitative and quantitative methods, provided a simple

**Table 1** - Classification of mucopolysaccharidoses.

MPS	Name	Increased GAGs	Inheritance	Enzyme deficiency	Gene location
I	Hurler, Hurler-Scheie or Scheie	HS + DS	autosomal recessive	$\alpha$ -duronidase	4p16.3
II	Hunter	HS + DS	X-linked recessive	Iduronate sulfatase	Xq28
III A	Sanfilippo A	HS	autosomal recessive	Heparan-N-sulfatase	17q25.3
III B	Sanfilippo B	HS	autosomal recessive	$\alpha$ -N-acetylglucosaminidase	17q21.1
III C	Sanfilippo C	HS	autosomal recessive	AcetylCoA $\alpha$ - glucosamine acetyltransferase	14p21
III D	Sanfilippo D	HS	autosomal recessive	N-acetylglucosamine 6-sulfatase	12q14
IV A	Morquio A	KS	autosomal recessive	Galactosamine-6-sulfate sulfatase	16q24.3
IV B	Morquio B	KS	autosomal recessive	$\beta$ -galactosidase	3p21.3
(V)	Scheie syndrome, initially proposed as type V, was recognized to be the attenuated end of the MPS I spectrum				
VI	Maroteaus-Lamy	DS	autosomal recessive	N-acetylgalactamine 4-sulfatase	5q11-q13
VII	Sly	HS + DS	autosomal recessive	$\beta$ -glucuronidase	7q21.11
(VIII)	An enzyme defect was found and proposed as MPS VIII, but shortly thereafter recognized as a laboratory pitfall; the proposal was withdrawn				
IX	Natowicz	Hyaluronan	autosomal recessive	Hyaluronidase 1	3p21.3

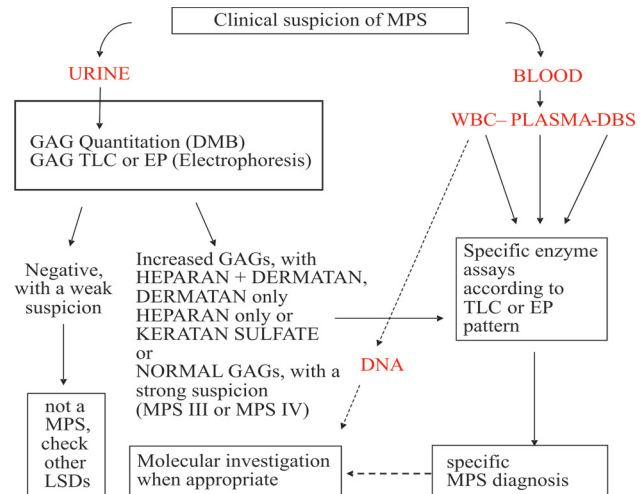
screening test for these diseases (Pennock, 1976; Piraud *et al.*, 1993). Even though the identification of the predominant types of GAGs excreted in urine provides important additional information about the most probable MPS type, the final diagnosis is based on the identification of the specific enzyme deficiency. This could be achieved by analysis using cultured fibroblasts, plasma or peripheral blood leukocytes, the last one usually being the preferred material for the test. The use of dried blood spots (DBS) as enzyme source is increasingly being used (Civallero *et al.*, 2006), but it is still recommended that positive results obtained using DBS are confirmed through leucocyte analysis.

The identification of the gene defect is not required for diagnosis (whenever the enzyme assay is available) but can be helpful for phenotype prediction and for the identification of carriers. Carriers frequently exhibit an enzyme activity in between the ranges of affected patients and normal controls, but some overlap is usually observed (Schwartz *et al.*, 2009). Carrier identification by genetic analysis is particularly important for MPS II, the X-linked form of MPS, to allow appropriate genetic counseling.

Prenatal diagnosis for MPS was performed even before the enzyme deficiencies were identified, as increased GAGs could be detected in the amniotic fluid of affected fetuses (Fratantoni *et al.*, 1969) in families which had a previous MPS case. However, this method was not generally reliable and was not applicable to all MPS (*e.g.* Morquio disease). Much more accurate prenatal diagnosis became available once the enzyme defects were known, and amniotic fluid cells, chorionic villi or cord blood could be used as a source for measuring enzyme activity. Molecular analysis could now be helpful in providing faster results in families where a mutation has already been identified in an index case. Figure 2 presents a suggested flow-chart for the diagnosis of MPS using blood and urine samples.

## The Road to Therapy

Although attempts to treat MPS diseases have been made with plasmapheresis (Lasser *et al.*, 1975; Nishioka *et al.*, 1979) and vitamin A supplementation (Wannmacher *et al.*, 1984), the first therapeutic approach which proved to bring benefits was bone marrow transplantation (BMT) (Hobbs *et al.*, 1981). The replacement of a patient's bone marrow cells by donor cells with higher enzyme activity is usually followed by a decrease in urinary GAGs, reduction of liver and spleen volumes and improvements in respiratory and cardiac parameters in some MPS types (mainly in MPS I and MPS VI, and potentially MPS VII). BMT (or Hematopoietic Stem Cell Transplantation, HSCT) is not considered beneficial for MPS III and MPS IV, and there is insufficient information about the outcome for MPS II. As mortality and morbidity are high, it is usually not recommended for MPS VI, as for this disease a treatment with enzyme replacement therapy (ERT) is available. The main present indication for BMT/HSCT is in the severe form of



**Figure 2** - Proposed flow-chart for the laboratory diagnosis of MPS (dashed line indicates that test is optional for diagnosis). MPS - mucopolysaccharidosis; GAGs - glycosaminoglycans; LSDs - lysosomal storage diseases; DMB - Dimethyleneblue (method used for GAG quantitation); TLC - thin layer chromatography; EP - electrophoresis; WBC - white blood cells; DBS - dried blood spots.

MPS I. In such cases, when BMT/HSCT is performed before the age of two years, donor cells could still migrate to the CNS and produce some enzyme locally, thus preventing the cognitive decline (Prasad and Kurtzberg, 2010).

A major breakthrough in MPS therapy was the development of enzyme replacement therapies for MPS I (Wraith *et al.*, 2004), MPS VI (Harmatz *et al.*, 2006), MPS II (Muenzer *et al.*, 2006) and now for MPS IV A (clinical trials in progress). Although these therapies do not provide a complete cure, the intravenous weekly administration of a recombinant enzyme similar to the missing one brings about measurable and sustainable benefits to the affected patients (Harmatz *et al.*, 2008; Clarke *et al.*, 2009; Muenzer *et al.*, 2011).

## Approaching the Remaining Challenges

Intravenous ERT markedly decreases urinary GAGs, reduces visceromegaly, improves joint mobility, improves respiratory function, decreases storage in heart muscle, increases growth rate, and improves endurance, among other benefits. However, the enzyme does not remove corneal opacity, does not significantly modify the bone disease, and also has a little impact on cardiac valves. Also, since the intravenously delivered enzyme does not cross the blood-brain barrier in significant amount, it does not address the spinal cord compression and cognitive decline present in the severe forms of MPS I and MPS II, and is also not an option for the treatment of MPS III patients.

To address the CNS manifestations, intrathecal ERT was tested in animal models, with promising results. Pioneer reports on intrathecal ERT to treat spinal cord compression in MPS I and MPS VI were made by our group (Munoz-Rojas *et al.*, 2008; Muñoz-Rojas *et al.*, 2010).

These cases opened the door for clinical trials with intratechal ERT to treat the cognitive decline on MPS I, MPS II and MPS III A (in progress).

Another approach has been the attempt to reduce the build up of GAG storage with the use of genistein, an isoflavone which interferes with GAG synthesis (Piotrowska *et al.*, 2006). Experiments *in vitro* and with animal models were quite promising, but preliminary results in patients using a relatively low dose did not show measurable benefits (Delgadillo *et al.*, 2011). Clinical trials are presently in progress using higher doses of genistein, and also using other substrate reduction therapy approaches.

Certain observations have led to the proposal that the administration of gentamycin would enable the cellular translation machinery to produce a full-length protein despite the presence of a premature stop codon (Hein *et al.*, 2004). This process, called “read-through”, is being explored with other agents and may be an option to modify the severe phenotype usually associated with non-sense mutations to a milder forms.

Gene therapy is also being developed for the MPS, with the view of providing the patient with the correct genetic information for the making of a normal enzyme, and in the near future this approach is expected to progress from pre-clinical studies to clinical trials (Ponder and Haskins, 2007).

The use of encapsulated cells which over-express the deficient enzyme, presently in preclinical development, may be an alternative method for providing an enzyme supply directly to the CNS (Matte *et al.*, 2011). In addition, this treatment could potentially replace the weekly infusions associated with intravenous ERT (Baldo *et al.*, 2012; Piller Puicher *et al.*, 2012).

### Early Diagnosis and Newborn Screening

There is evidence that storage of GAGs begins very early in life (Baldo *et al.*, 2011), and that this storage triggers a cascade of pathogenic events (Bellettato and Scarpa, 2010; Vitner *et al.*, 2010), a process that, once started, could be difficult to reverse. The experience of many doctors suggests that early diagnosis and early treatment bring a better outcome for the MPS patient. This impression has been elegantly documented by McGill *et al.* (2010) for two MPS VI sibs, and by Gabrielli *et al.* (2010) for two MPS I sibs. In both reports, one sib was started on the ERT earlier than the other, and observations made when the patients were at the same age indicated a better outcome for the early-treated sib compared to the late-treated one.

These observations, along with the development of high-throughput methods for enzyme analysis using dried blood spots (Wang *et al.*, 2005) or the analysis of GAG species in urine samples (Auray-Blais *et al.*, 2011) are fueling the proposals to initiate newborn screening for MPS diseases, with pilot programs presently being planned. A pilot newborn screening program for MPS VI in a high-incidence

area of northeastern Brazil is presently in progress and should provide important information about the feasibility of these initiatives.

### The MPS Brazil Network

The rarity of the MPS and the relatively sophisticated methods required for their diagnosis presents a challenge to clinicians attempting to identify and manage these conditions, especially in developing countries. An interesting and innovative project to improve the access of families and health professionals to information, diagnosis and treatment of MPS was set up in Brazil. The MPS Brazil Network is a partnership among medical services in Brazil which deal with MPS patients. The network has a webpage ([www.mps.ufrgs.br](http://www.mps.ufrgs.br)) which provides a wide range of information and is also a tool for the request of diagnostic tests, which are performed in the network laboratories. A toll-free telephone information service is also in operation, and regular meetings are held to keep families updated with the most recent advances in the field. This initiative is supported with public and private grants, which enable it to provide the services free of charge, making information and diagnostic tests available even for families that usually do not have access to sophisticated healthcare facilities. The consequence of this was that during its first seven years of operation (March/2004 to April/2010) the MPS Brazil Network was able to diagnose over 500 new cases of MPS in Brazil (Table 2), doubling the previous rate of diagnosis.

### Final Remarks

During the last hundred years, remarkable progress has been made in the clinical, biochemical and molecular characterization of the MPS, leading to successful preventive and therapeutic approaches. Despite the recent advances, especially with enzyme replacement therapy

**Table 2** - Diagnosis of new cases of MPS by the MPS BRAZIL NETWORK among 2,606 patients investigated between 2004 and 2011 (8 years).

MPS type	Number of cases
MPS I	92
MPS II	160
MPS III A	24
MPS III B	34
MPS III C	21
MPS III D	0
MPS IV A	49
MPS IV B	4
MPS VI	118
MPS VII	6
MPS IX	0
Total	502

developed for several MPS types, some challenges still remain. One major difficulty is how to address the CNS manifestations; another is how to reverse the pathology in hard tissues like bone and heart valves. Progress on the understanding of the physiopathology of these diseases and more advanced treatment approaches such as intratechal ERT, substrate reduction therapy, read-through approach, gene therapy, or therapy using encapsulated modified cells will certainly provide a future for these patients. As early diagnosis and early treatment seem to provide a better outcome, newborn screening may also play an important role in reducing the impact of these diseases.

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