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MUCOPOLYSACCHARIDOSIS TYPE II (MPS II) IN LATIN AMERICA

The case of Brazil

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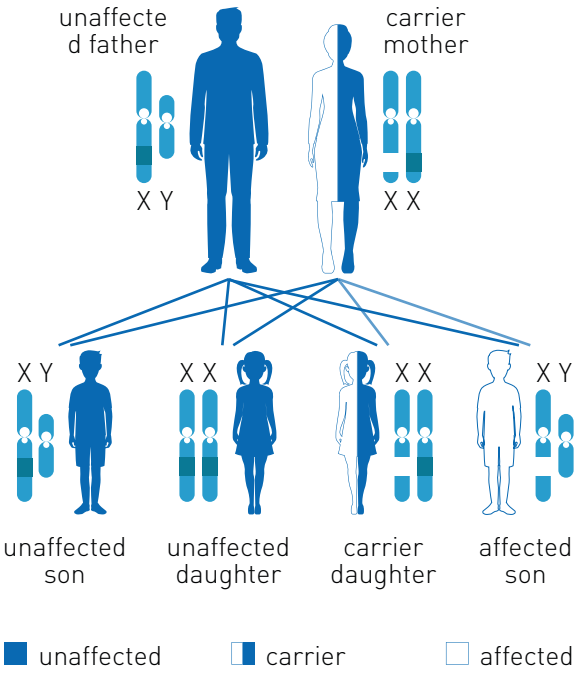
A brief introduction of Mucopolysaccharidosis type II

Mucopolysaccharidosis (MPS) are genetic disorders caused by specific lysosomal enzyme deficiencies, leading to the accumulation of glycosaminoglycans (GAGs) – long chains of sugars (carbohydrates)– in the extracellular matrix and cells. The increase of the GAGs deposits ends up compromising tissues and causing organ malfunction (Khan et al. 2017).

Currently, MPS is a disease categorized in seven clinical types (and numerous subtypes) in accordance with the specific lysosomal enzyme affected, leading to variable phenotypes, severity, and progression patterns among MPS types (Neufeld and Muenzer 2001).

In this white paper, a vision of the MPS type II landscape in Latin America, with an emphasis in Brazil, will be addressed.

X-linked recessive inheritance



MPS type II (also called Hunter syndrome) is caused by lack of the enzyme iduronate-2-sulfatase.

This clinical type is the only MPS disorder in which the mother alone can pass the defective gene to a son (called X-linked recessive).

The disease is almost exclusively found in young males (Khan et al. 2017).

The neuronopathic phenotypes are more prevalent than non-neuronopathic, such that about 2/3 of MPS type II patients have neurodegeneration. This decline involves IQ loss and skills regression and, in some types, intense behavioral abnormality which affects patients' lives as well as their family members (Antoine Daher President of Casa Hunter and Febrararas)

Chapter 1
The Scenario in Latin America

In Latin America, the MPS type II landscape is different from the one in US. The incidence in Latin America ranges between 0.69 to 1.19 cases in 100,000 live births (Giugliani et al. 2014).

Furthermore, the awareness in Latin America for this disease is weak and patient management as well as early diagnosis are still major challenges in the region.

Currently, Brazil is a reference in the region due to their increased experience on dealing with the disorder. However, all Latin America countries still face unmet needs due to the absence of an effective treatment for neurodegenerative disease progression and other obstacles on dealing with the disease.

In Brazil, MPS type II is the most common clinical type, accounting for approximately 30-40% of the MPS disorders (Khan et al. 2017). From 2000 until 2020, there have been around 400 diagnosed patients in Brazil, with an incidence of 10- 15 per year. While in Colombia MPS type II is also the most frequent of the MPS disorders, in Argentina and Mexico that is not the case; in the later, MPS type IV is the most common.

Whereas the majority of the MPS type II cases are known in Brazil, in other Latin America countries this does not happen. Professor Roberto Giugliani mentioned that in Peru "most of the cases are not diagnosed", while in Chile "there is a lack of specialized laboratories to perform the genetic test" and in Colombia "genetic testing is very expensive".

The same HCP mentioned that Brazil is an informal reference in diagnostics for MPS type II in the region stating that "some Latin America countries send to Brazil patient samples in order to be performed the genetic testing for diagnosis". Although the diagnosis of the MPS type II disorder is a major problem for most of Latin America countries, there are other unmet needs to overcome.

Regarding MPS type II treatment, although Brazilian Minister of Health started to reimburse the available treatment in January 2019 (CONITEC decision was published in December 2017), most of the Latin American countries still lack access to it.

However, the treatment available provides a limited therapeutical benefit, since a large proportion of the patients present the neuronopathic phenotype which is not addressed by this therapeutic option.

In addition, patient needs to be followed by a multidisciplinary team. Concerning this topic, Professor Roberto Giugliani mentioned that "*the treatment is coordinated by the geneticist, but patients undergo multiple organ failures and need a multidisciplinary team composed of neurologist, cardiologist, physiotherapist and other specialized Healthcare Professionals*".

1.1. The value of Clinical Trials in Latin America

Implementation of Clinical Trials in Latin America are particularly important not only for the development of the internal capability and improvement of knowledge by the experts in the country but also to attract local investments and offer patients an early access to innovative approaches to tackle MPS type II disease progression.

The access pathway for Latin American countries is very lengthy, so patients usually go to the Court to request treatment access. In Brazil, the situation only changed in 2019, when the government started to deliver MPS type II treatment for free to patients.

A new research treatment for MPS type II started in Brazil 3 years ago. Through this research, patients have been able to access for an innovative treatment, bringing to clinicians a solution for an unmet need.

"This new product under development demonstrated a huge difference for the patients, since it is addressing both somatic and neurocognitive symptoms. Patients that do not sleep well and who are not able to seat into the table for a meal or have lost the capability to speak, after more than 2 years under the clinical trial, can sleep better, seat into a restaurant table to eat, understand parent's simple commands and have also started to speak". Mr. Daher also said: *"People that do not understand the impact of the disease for the patients and families, cannot imagine the improvement that our patients and families achieved with this new product"*.

The participation of other Latin American countries in clinical trials would expand the access to new and notable treatments for the disease, especially on low-income populations and with limited access to healthcare treatments.

1.2. Brazil as an informal reference in Latin America

MPS type II disease management is an exceptionally important issue for the patients. Due to the significant experience on dealing with this disease, Brazil has become a reference in Latin America.

1.2.1 Diagnosis and Therapeutic access

The presence of diagnostic centers and the high experience on dealing with the disease encourages several Latin American countries to send their patients to Brazil to run diagnostic tests for MPS type II.

Furthermore, in the portfolio available to tackle the disease, Brazil possesses the enzyme replacing therapy to offer to these patients. Regarding healthcare awareness to the disease, it was created the Interministerial Committee on Rare Diseases. The committee will work to develop policies that result in a better quality of life for people with rare diseases. It will also formulates strategies for the collection, processing, systematization and dissemination of information about these diseases, in addition to encouraging the network of specialized centers, reference hospitals and other places of care for people with rare diseases in the public network.

1.2.2 Healthcare policies on rare diseases

One of the reasons for Brazilian favorable landscape on dealing with MPS type II disease comes from political engagement in developing new tools for rare diseases.

Legislation effort was placed on rare diseases through the published government ordinance in PORTARIA Nº 199 (2014) and by ANVISA (Brazilian medicine agency) prioritization of the research on rare diseases.

This favorable legislation landscape for rare diseases promoted the incorporation of the enzyme replacement therapy for MPS type II disease into the public healthcare system in 2017 (CONITEC 2017). Additionally, ANVISA registered advanced genetic therapies in December 2018 which defines the procedures and regulatory requirements for carrying out clinical trials with investigational advanced therapy product in Brazil. This is a step further that allows patients to have access to other advanced therapies for MPS type II, which are under development.

In Brazil, MPS is not part of newborn screening test, reimbursed by the government. The incorporation of the disease into the test would speed up access to the treatment and 2/3 of diagnosed patients could avoid a neurodegenerative damage, a consequence observed in severe cases.

This situation can be solved in Brazil soon, if the Law 14.154/2021 (LP 5043/2020) approved by President Bolsonaro on June 26th, 2021, will be implemented from June 2022 on to include several genetic diseases, as MPS. This will allow faster access to treatment after the diagnosis, avoiding irreversible neurological damages and early deaths.

1.2.3 Patient Advocacy

Casa Hunter, as a non-profitable foundation, plays a distinctive role on MPS type II by the cooperation between healthcare practitioners and families on the landscape of MPS type II in Brazil, as well as their influence on public policies regarding the disease.

Through their raised funds, Casa Hunter is developing a secure genetic therapy for MPS type II as well as is building "Casa dos Raros" in partnership with IGPT (Genetic Institute for all) and MD Roberto Giugliani. This is the first institute in Latin America specialized in multidisciplinary treatment of the patients with rare diseases from SUS or private sector.

Additionally, with the implementation of the Hunter Day Project in several Hospitals in different states, Casa Hunter assists families and patients with a multidisciplinary team raising the importance of a multidisciplinary approach for the treatment.

Although Brazil is a reference in Latin America for MPS type II, there are unmet needs to overcome. The President of Casa Hunter and Febrararas, Dr. Antoine Daher, mentioned the lack of support to families and patients: *"the family burden is very heavy. There is a need for weekly infusions at specialized centers for the treatment. For those who live far from the specialized treatment centers, the logistics brings a huge financial impact to the families"*.

Overall, the experience on the disease and the available treatments makes Brazil high ranked in Latin America as a reference to MPS type II disease management.

Chapter 2
Implementation of possible solutions

In the context of rare diseases, the implementation of possible solutions is seldom a simple and immediate exercise.

This is coupled with the associated challenge of trying to design and implement such solutions in a country like Brazil, with an almost continental geographical scale, an economic and social context under great pressure, a health system with limited capacities to respond to rare disease patients and their families, and sub-optimal access to innovative treatments.

It is based on these realities that we seek to present below a set of alternatives that, individually or, ideally, in combination, can be implemented to improve the responsiveness in diagnosis, treatment, and follow-up of patients with MPS type II, and their families.

2.1. Disease awareness to students attending Medical Schools

During the university period, students attending medical courses in Brazil only have genetic classes during the 1st year. Such fact strongly limits their ability to get a thorough education and training related to rare diseases and genetic disorders, likely to hamper their ability to identify or diagnose a patient.

Invest to improve medical education, or at least raise rare disease awareness within this key population, might make progress and lower the average 5 years of rare disease patients to be diagnosed. With the improvement in the training of physicians, especially in primary care, patients and families will profit because they begin to have access to the necessary treatments earlier as the diagnosis is made in a timely manner and, hopefully, improve their quality of life.

2.2. Disease awareness to pediatricians and geneticists

Although there are efforts on physician education for rare diseases, there is still room to develop the disease awareness on those specialties which manage MPS type II, namely, pediatricians and geneticists.

In Brazil, most of the patients are located outside main cities which demand further improvements on physicians' education and support to use and adopt new treatments; updated scientific and clinical information on rare diseases.

2.3. Awareness of patients' associations

Most of the work on updating the physicians for MPS type II is performed by the pharmaceutical industry. As a representative of the population that suffers from the disease, patients' associations need to be involved in the education and devotion to raise the awareness of the pediatricians and geneticists for the problem.

2.4. Physician guidance to diagnostic tools and reimbursement

In Brazil, physicians do not usually know how to perform the diagnostics. Frequently, it is up to the industry to support the diagnostics of MPS type II. In this respect, there is a need to support and educate physicians about diagnostics tools and procedures, as well as how to conduct them. Physicians should also be aware of the list of tests and procedures already covered by the government and how to access it, fulfilling all requirements to provide the access for patients.

2.5. Improved access to diagnostics

About 2/3 of the patients with MPS type II in Brazil suffer from progressive neurological impairments. Due to this, there is a need for an improved and faster disease diagnostic procedure, allowing them to have access to the treatment in the early stages, to control disease progression. The Law 14.154/21 mentioned above for the incorporation of the MPS type II in newborn testing is set to help but may prove not to be enough or come in time for many new patients.

Unfortunately, the Law did not establish a deadline for the implementation of each stage of the expand newborn screening and considering MPS was classified in the 3rd stage, it is not clear, when government will include it into the newborn screening national policy.

However, as already mentioned, the diagnostics of MPS II by newborn screening test, can avoid irreversible neurological damages and early deaths.

For this reason, it is extremely important that patient groups and medical Societies, KOLs, Congress members and many others require a fast implementation of all newborn screenings tests, to prevent irreversible damages to rare disease patients and their families.

2.6. New treatment centers

There's a need for the creation of new Reference Centers in Brazil to manage Rare Diseases according to the most prevalent geographical areas. These centers need to have multidisciplinary teams to access different features of the disease progression. The existing centers are scarce and located far from the disease 'hot-spots', negatively impacting patients and families by increasing their burden. ("Interfarma 2021" paper).

2.7. Increase awareness of healthcare managers

Due to the low number of patients enrolled in rare diseases studies, it is hard to obtain statistical meaning on clinical trials data for hard end endpoints.

However, other outcomes of clinical trials should be available for decision making on treatment approval, and HTA process. Perhaps, they should have a look at surrogate endpoints on patient progression based for instance on biomarkers concentration in CSF, plasma or urine. Medical literature clearly demonstrates the correlation between reduced concentrations of biomarkers (substrates) with the stabilization or improvement of clinical parameters captured by serial neurocognitive assessments.

2.8. Promotion of other models for treatment access

Most patients (≈75%) are within the public healthcare system while the remaining are part of the private system. However, both systems contribute for almost the same amount of the GDP in Brazilian healthcare.

In terms of treatment approval, rare diseases are mainly covered by public system. Then, new models, especially in rare diseases, such as risk-sharing, QALY measurement, MCDA (multi criteria for decision analysis) and many others already implemented in other countries, should be incorporated in public healthcare system. This may cause less hurdles for improved treatments and eventually triggers less impact in healthcare systems.

Conclusions

The scenario in MPS type II disease management in Brazil is at a better stage when compared to other countries in Latin America. However, due to the growing number of patients, the size of the country and the new treatments under registration process to address an unmet need for the disease, there is a lot to do, as explained below.

The greatest hurdle to prevention, diagnosis and treatment of a rare disease is lack of, or limited knowledge. Scientific knowledge is urgently needed to understand the causes and other mechanisms that will result in delays in the diagnosis and inappropriate treatment, whether drug therapy or other medical attention.

Patients go often to public hospitals and services throughout their undiagnosed period (an average of 5-8 years) to treat several morbidities and problems related to MPS symptoms. However, due to the lack of specialized physician training, there is no historical investigation to understand the cause of the recurrent problems from those patients. In addition, it is the public healthcare system that deals with most of the patients suffering from rare diseases. Yet, public policies do not follow the pace of treatment innovations.

To circumvent the problem in public healthcare systems on dealing with rare diseases, there is a need for raising awareness to primary care physicians and other multidisciplinary professionals to recognize that a specific patient could have a rare disease. After, the patient needs to be referred to a reference center, where there will be specialists to provide the proper diagnosis and treatment.

Regarding access to new technologies for rare disease management, Minister of Health should change current law to allow the implementation of new market access models that will for sure support the country to include new diagnostics and treatments at early stages of disease progression.

Rare disease management is complex and has a high cost for the government. Using other countries as a reference, pharmaceutical industry needs to be a major player regarding decision making, as part of the solution, and this can improve the outcomes, addressing unmet medical needs.

It's also important to mention that in Brazil the decision should be part of a multitask group composed by the government, patients, medical societies, key specialists, Academia, and Pharma industry, once together they can find a better solution for patients and for the country.

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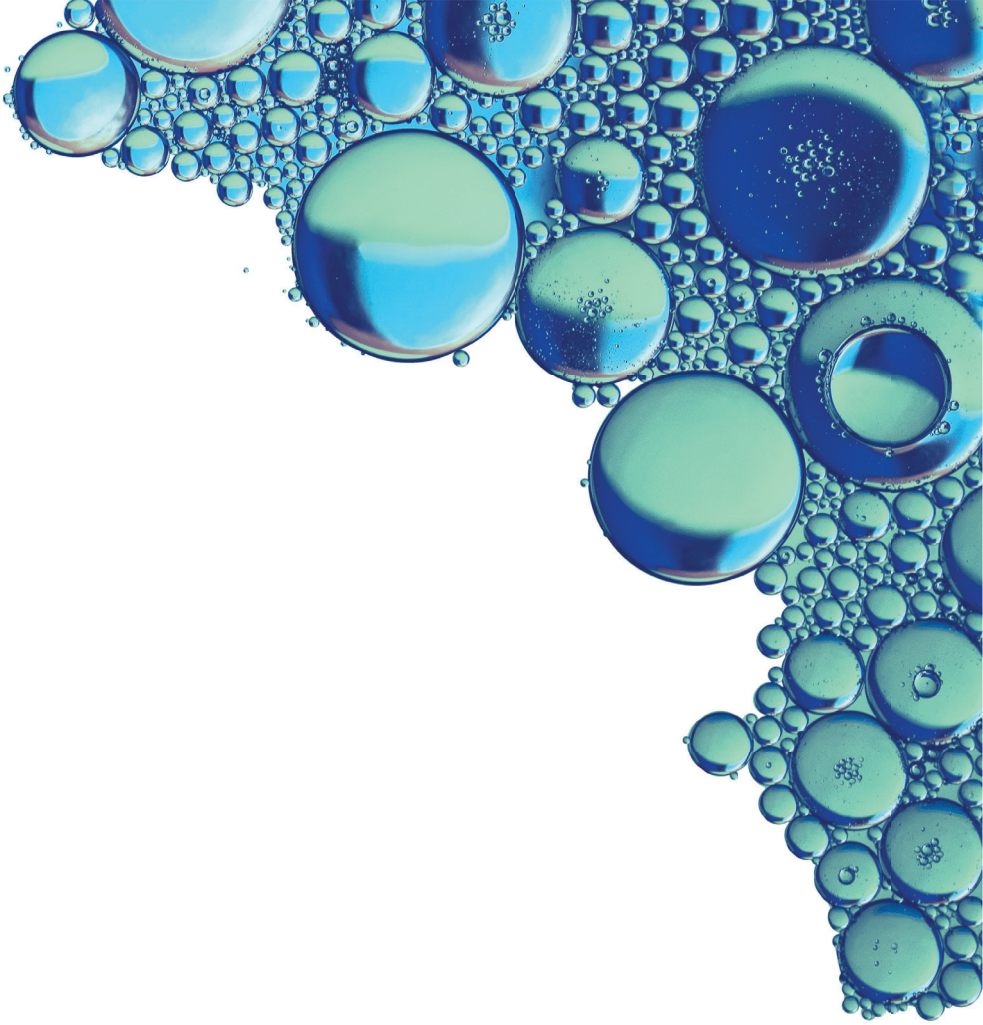

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