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Original Research Paper

Epidemiology

MUCOPOLYSACCHARIDOSIS TYPE 2: NARRATIVE REVIEW

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ABSTRACT Mucopolysaccharidosis type II, also known as Hunter syndrome, is a rare, progressive, multisystemic lysosomal storage disease caused by deficiency of iduronate 2 sulfatase, an enzyme responsible for the degradation of the mucopolysaccharides dermatan (DS) and keratan sulfate (QS), causing their accumulation at the lysosomal level. It is an X-linked disease, therefore it is common to find most cases in men, rarely in women, it is considered an orphan disease given an incidence of approximately 1/100,000 live births. Various phenotypes of severe (2/3) and attenuated disease have been described. The diagnosis is based on clinical findings and the measurement of mucopolysaccharides DS and QS in urine, which are elevated, confirmed by determining the enzyme deficiency in serum, leukocytes and fibroblasts. It has been observed that in patients with enzyme replacement therapy somatic symptoms have decreased, however there are several studies of alternative therapies in the future, including gene therapy as an alternative in the future.

KEYWORDS : Hunter syndrome, iduronate-2-sulphatase, lysosomal storage disease, mucopolysaccharidosis type II, skeletal–muscle system.

INTRODUCTION

Mucopolysaccharidoses type II (MPS II) is part of the group of lysosomal storage disorders, about 7 types of mucopolysaccharidoses have been described. MPS II was first described around 1917 by Charles Hunter with the clinical observation of 2 brothers with characteristic features, long confused with a similar condition known as Hurler's syndrome (severe form of mucopolysaccharidosis type 1). has been distinguished as a specific disease since 1978 by identifying the genetic causes of both diseases in a publication by Lorincz (2), MPS II is the only hereditary mucopolysaccharidosis linked to the X chromosome with a recessive pattern of inheritance. It is caused by a deficiency of the lysosomal enzyme iduronate 2-sulfatase responsible for the degradation of the mucopolysaccharides dermatan and keratan sulfate. The IDS gene is mapped to the chromosomal region Xq28, covers 44 kb and is structured in nine exons (1). The enzyme deficiency produces dysfunction of most organs and systems, which translates into a severe clinical phenotype. Children with severe form are usually diagnosed between 12-36 months of age, these patients are characterized by having, among others: short stature, coarse facial features, short neck, wide chest, large head circumference, behavioral changes, delayed progressive mental illness and alterations of the respiratory, cardiovascular, musculoskeletal and nervous systems (3).

Methods

This narrative review was based on a search strategy that was carried out in databases such as PubMed/Medline, Lilacs and Redalyc, EBSCO. The MeSH and DeCS thesauri were used. Articles such as clinical trials, systematic reviews, topic reviews between the years of 1949 and 2022 were included.

Epidemiology

Various publications agree that the incidence of MPS II is approximately 1/100,000 live births, since it is an X-linked disorder, it is common for most cases to occur in men, studies have been carried out in various countries, Brazil reports an incidence of MSP II of around 0.38/100,000 live births, in contrast, Portugal has described rates of 1.09/100,000 live NBs. In general, European countries have a lower incidence compared to Asian countries, where in some of them, for example, Taiwan, the incidence reaches up to 2.05/100,000

live NBs and where MPS II represents around 50% of all deaths. mucopolysaccharidoses (4). In Colombia, an approximate frequency of 1.98/100,000 live NB has been estimated for all mucopolysaccharidoses, with a predominance of type IV (5). A diagnosis peak of the disease has been seen around 24-48 months of age, where the clinical manifestations, mainly somatic, are evident, leading to suspicion of the disease and for which specific studies for its diagnosis are initiated.

Clinical Manifestations:

MPS II tends to affect multiple organs and systems, within the general manifestations characteristic signs of the disease have been described that are shared regardless of the severity of the presentation, within them are: growth retardation, short stature, facial features skeletal deformities, joint stiffness, valve disease, organomegaly (mainly spleen and liver), ENT manifestations (hearing loss, tonsillar hypertrophy, and sleep disorders including obstructive apnea) (6).

Nervous system

The accumulation of heparan sulfate in brain tissue is proportional to the accumulation of secondary molecules, mainly gangliosides (GM2 and GM3), with subsequent activation of microglia, which triggers the inflammatory response in the brain, the attenuated and severe phenotypes of the disease. depend on whether or not there is CNS involvement, hydrocephalus usually occurs before any behavioral change, it has been seen that child with MPS II do not show alterations until around 3-4 years of age, when it begins to show a cognitive deficit, with difficulty in developing language skills, this is also related to conductive deafness, recurrent ear infections and in some cases deformities of the ossicles (7,8).

Cardiovascular System

Cardiovascular diseases in patients with MPS II are the main cause of premature death, among which valvular heart disease, left ventricular hypertrophy and alterations of the conduction system stand out.

Heart valve disease is the most common manifestation (60-90%) of patients with MPS II. It has been seen that valve insufficiency is more common with greater involvement of the left side of the heart (mitral and aortic), with the mitral valve being the most compromised (9,11, 12).

Respiratory System

The deposition of GAG in the soft tissues of the respiratory tract, mainly in the trachea and throat, leads to a narrowing of the same which hinders the flow of air to the lungs. This restrictive disease is exacerbated by rib cage deformities secondary to concomitant bone and joint involvement.

Sleep apnea is a common diagnosis in MPS II patients, probably due to tracheal narrowing, thickened vocal cords, and hypertrophied tonsils and adenoids (13).

Diagnosis

The diagnosis of MPS II is a challenge given its similarities with other types of mucopolysaccharidosis and the lack of standardization of tests for its diagnosis. Once the patient with features that suggest MPS II has been identified, specific tests are carried out to give a certain diagnosis of the disease. The first step is the analysis of mucopolysaccharides in 24-hour urine, either by a quantitative test, and if a qualitative test is available (6). The second step is to carry out a fractionation method to determine which mucopolysaccharide is predominant. This can be done by means of chromatography or protein electrophoresis (7). Diagnosis is confirmed by demonstration of specific enzyme deficiency, urine results guide enzyme analysis, sample for enzyme assay can be drawn from leukocytes or fibroblasts, MPS II is understood to be a more difficult assay to carry out since the use of radioactive substrates is required, in addition to laboratories with experience in its realization. The third step consists of carrying out genetic and molecular tests to identify the genetic variant causing the disease, including PCR amplification of the IDS exons with subsequent Sanger sequencing. In general, PCR is also useful to show partial or complete deletions. In certain cases it is necessary to carry out additional analysis, for example mRNA or comparative genomic hybridization to detect large deletions and/or duplications (8,14,15).

Treatment:

Hormone Replacement Therapy (ERT)

The treatment of conventional MPS II has been enzyme replacement therapy (ERT), in said therapy the recombinant enzyme IDS (iduronate 2 sulfatase) is administered intravenously on a weekly basis, a review of the efficacy of intravenous therapy showed that patients who received at least one year of therapy had improvement in somatic symptoms, a decrease in the frequency of respiratory infections and improvement in joint movement, as well as a decrease in coarse facial features, however ERT does not seem to alter the neurological deterioration of the disease (16).

The therapy is offered to all patients if they are not in end-stage disease and should be continued unless ineffective after 6 months, based on clinical improvement (17).

Bone Marrow Transplant (HSCT)

The principle of hematopoietic stem cell transplantation (HSCT) is based on providing a cross-correction of enzymes in deficient tissues, however it must be remembered that there is a risk of developing graft-versus-host disease, for which donors must pass through a rigorous selection process.

Its main efficacy has been seen in the normalization of organomegaly, improvement of valvular heart disease and increased joint elasticity, with subsequent improvement in the patient's quality of life (17).

REFERENCES

1. D'Avanzo, et al(2020). Mucopolisacaridosis tipo II: cien años de investigación, diagnóstico y tratamiento. Revista internacional de ciencias moleculares , 21 (4), 1258.
2. Tylki-Szyma ska A. (2014). Mucopolysaccharidosis type II, Hunter's syndrome. Pediatric endocrinology reviews : PER, 12 Suppl 1, 107–113.
3. Lorincz AE. Las mucopolisacaridosis: Avances en su comprensión y tratamiento. pediatra Ana. 1978; 7 :104–122.
4. Lin, H. Y., et al. Clinical characteristics and surgical history of Taiwanese patients with mucopolysaccharidosis type II: data from the hunter outcome survey (HOS). *Orphanet journal of rare diseases*, *13*(1), 89.
5. Gómez, A. M., García-Robles, R., & Suárez-Obando, F. (2012). Estimación de las frecuencias de las mucopolisacaridosis y análisis de agrupamiento espacial en los departamentos de Cundinamarca y Boyacá. Biomédica, 32(4), 602-9.
6. Filocamo, M., et al. (2018). Análisis bioquímico y molecular en mucopolisacaridosis: lo que debe saber un pediatra. *Revista italiana de pediatría* , *44* (Suplemento 2), 129.
7. Mashima, R., Okuyama, T. y Ohira, M. (2020). Biomarcadores para trastornos de almacenamiento lisosomal con énfasis en espectrometría de masas. Revista internacional de ciencias moleculares , 21 (8), 2704.
8. Zanetti, A., et al. (2014). Un paciente de Hunter con un fenotipo grave revela dos deleciones grandes y dos duplicaciones que se extienden 1,2 Mb distalmente al locus IDS. *Informes JIMD* , *17* , 13–21.
9. Moreira, G. A., et al. Prevalence of obstructive sleep apnea in patients with mucopolysaccharidosis types I, II, and VI in a reference center. *Sleep & breathing = Schlaf & Atmung*, 2014; *18*(4), 791–797.
10. Morini, S. R., Steiner, C. E., & Gerson, L. B. (2010). Mucopolysaccharidosis type II: skeletal-muscle system involvement. *Journal of pediatric orthopedics. Part B*, *19*(4), 313–317.
11. Stapleton, M., et al. Presentación y tratamientos de la mucopolisacaridosis tipo II (MPS II; síndrome de Hunter). *Opinión de expertos sobre medicamentos huérfanos* , 2017; *5* (4), 295–307.
12. Braunlin, EA, et al. Enfermedad cardíaca en pacientes con mucopolisacaridosis: presentación, diagnóstico y manejo. *Revista de enfermedades metabólicas heredadas* , 2011; *34* (6), 1183–1197.
13. Leighton, S. E. Disordered breathing during sleep in patients with mucopolysaccharidoses. *International journal of pediatric otorhinolaryngology*, 2011;*58*(2), 127–138.
14. Jones, et al. Mortality and cause of death in mucopolysaccharidosis type II-a

historical review based on data from the Hunter Outcome Survey (HOS). *Journal of inherited metabolic disease*, 2009; *32*(4), 534–543.
15. Muenzer, J., et al. The role of enzyme replacement therapy in severe Hunter syndrome-an expert panel consensus. *European journal of pediatrics*, 2012; *171*(1), 181–188.
16. Scarpa, M., et al. Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease. *Orphanet journal of rare diseases*, 2011; *6*, 72.
17. Aldenhoven, M. Hematopoietic cell transplantation for mucopolysaccharidosis patients is safe and effective: results after implementation of international guidelines. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*, 2015; *21*(6), 1106–1109.