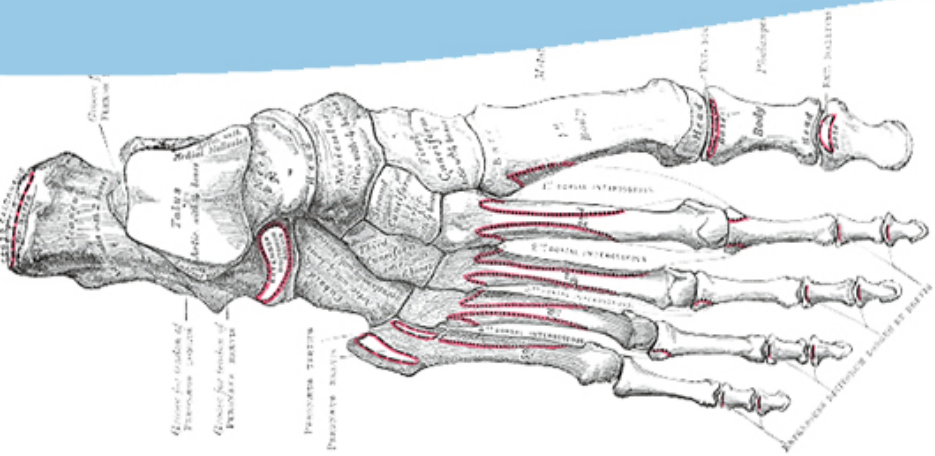

5. Revisión 3

Mucopolysaccharidosis type III: an updated review

by Laínez Ramos-Bossini, AJ
Medical Student, Faculty of Medicine, University of Granada, Spain.

Arch. Med. Univ. 2018, Nº5, ISNN: 2341-0361.

Abstract: This paper is aimed at revising the scientific literature about mucopolysaccharidosis type III in order to describe its main features. Firstly, the clinical presentation as well as the different phenotypes included in this syndrome are explained. Secondly, biochemical exams used in the specific diagnosis of this syndrome are reviewed. Also, key points related to early diagnosis, prenatal and genetics testings are highlighted. The role of pediatricians and primary care physicians as main actors in the patients' follow-up and the importance of other specialists depending on the patients' needs are assessed. Finally, current treatment options and experimental studies for new therapies are described. The most relevant aspects of MPS III are reviewed, facilitating the comprehension of this disease and thus making the readers aware of this challenge in medicine nowadays.

Resumen: El objetivo de este trabajo es revisar la literatura científica acerca de la mucopolisacaridosis tipo III con el fin de describir sus características principales. Así, se delimita el cuadro clínico y los fenotipos que se consideran a la hora de estudiar este síndrome. A continuación se analizan las pruebas bioquímicas que se llevan a cabo para el diagnóstico específico de esta patología. Posteriormente se revisan puntos clave del diagnóstico precoz y las pruebas actuales que permiten realizar el diagnóstico prenatal y las pruebas genéticas. Igualmente se establece el papel del pediatra y del médico de atención primaria como pilares principales en el seguimiento del paciente así como la importancia de otros especialistas en función de las necesidades de este. Por último, se describen las opciones de tratamiento existentes en el momento actual y las terapias en vías experimentales de mayor relevancia. De este modo, evaluaremos los puntos más importantes de la enfermedad, a fin de facilitar no solo la comprensión de la misma, sino también

procurando que el lector conozca el reto que supone esta patología para la medicina en la actualidad.

Keywords:Mucopolysaccharidosis type III, Sanfilippo syndrome, glycosaminoglycans, developmental delay.

Palabras clave: Mucopolisacaridosis tipo III, síndrome de Sanfilippo, glicosaminoglicanos, retraso en el desarrollo.

Introduction

The mucopolysaccharidoses (MPS) are a group of seven hereditary metabolic diseases characterized by a total or partial deficit of a lysosomal enzyme (1), with subsequent accumulation of molecules in the lysosomes that cells can not digest. In the case of mucopolysaccharidoses, the molecules accumulated are glycosaminoglycans (GAG), that are part of the connective tissue. Given the ubiquitous presence of this tissue in the body, these diseases have a multisystemic impact.

MPS III or Sanfilippo syndrome is the most frequent MPS (2). It is transmitted with a recessive autosomic pattern and it is caused by a defect in the enzymatic degradation of heparan sulfate (1,3). There are four subtypes of MPS III depending on the enzyme affected: A (heparan N-sulfatase deficiency, the most severe form), B (α–N-acetylglucosaminidase deficiency), C (acetyl-CoA-α-glucosamide-acetyltransferase deficiency) and D (N-acetyl-glucosamine-6-sulfatase deficiency) (1).

The incidence of this disease is estimated to be around 1 in every 70000 newborns, being A and B subtypes more frequent than C and D subtypes (3). Recently, a retrospective study was carried out in Spain to analyze the natural history of MPS III in 55 patients with the disease. The most common subtype was found to be MPS IIIA which accounted for more than half of the patients affected (4). Table 1 summarizes the most relevant aspects of each subtype of MPS III.

The present review highlights that, although MPS III is a rare disease, the clinician should always bear it in mind in the differential diagnosis of other less dramatic diseases, because its initial diagnosis is essentially clinical (3). The wide variety of signs and symptoms with which the disease may appear early obliges a comprehensive analysis so that the clinician does not ignore them.

Not only does the diagnostic algorythm matter; the follow-up is also extremely relevant because there are many stages of disease progression and the severity of the disease increases as the stages advance. Correct identification of these stages is required to apply the necessary protective or paliative treatments. The leading role of the pediatrician and the primary care physician in the multidisciplinary team is of extreme relevance during the patients follow-up. Several treatments have been tested with no curative outcomes. Although new therapies are currently explored, they still belong to the experimental field, and only paliative treatments are available for the MPS III.

Synthesis of the review

Symptoms

Signs and symptoms of MPS III are very heterogeneous, and its diagnosis is very difficult in comparison with the rest of MPS types, in which bone abnormalities usually appear at an early age, so they are diagnosed early. Besides, there are no pathognomonic signs, so that the absence of the signs described below does not allow to confirm the diagnosis. Common physical signs (see Table 2) include: increased head circumference, thick eyebrows, tongue protrusion, thick lips, increased amygdale volume, umbilical hernias and hirsutism. Hepatosplenomegaly and musculo-skeletal manifestations (scoliosis, lumbar lordosis, kyphosis, hip dysplasia, carpal tunnel syndrome, trigger finger) are not frequent (5).

The clinical manifestations of MPS III patients are essentially neurocognitive (6). Some studies have reported structural and functional defects of the blood-brain barrier which could explain these alterations (7). Developmental delay is usually the first sign that stands out. This de-

lay often affects language and it can be the sole sign noticed in the patient. For that reason it is frequent to misdiagnose an idiopathic language development instead of MPS III. Other patients show a more general affectation of development, so they are thought to suffer from the spectrum of autism or idiopathic language development (8).

After the developmental delay, the next clinical manifestations often are disturbed behaviour (see Table 2) and sleep disorders, which tend to appear in advanced stages of the disease. Besides, insomnia and nocturnal awakenings worsen the disturbed behaviour. Recent studies have shown that the blood concentration of melatonin in these patients correlates with disruption of the circadian rhythm. Therefore, treatments aimed to the synchronization of the circadian rhythm could be very useful (9).

Natural history

MPS III is a progressive disease with three different stages that emerge after an apparently normal development. Besides, depending on the degree of affectation, two phenotypes with different natural histories are distinguished: mild and severe ,Since the severe phenotype is the most frequent, its natural history will be described first, following the three stages into which the disease is divided.

In the first stage of the disease, which usually occurs between the first and the third year of age, a slowing down or detention of the cognitive development is observed. Motor development usually evolves in a natural way during this stage. Some characteristic physical signs as those described above may appear.

The second stage starts approximately at the third or fourth year and it is characterized by progressive cognitive impairment, disturbed behaviour, impulsiveness, obstinacy, anxious and autistic behaviour that get worse over time and can be of extreme intensity.

The third stage usually appears during the adolescence, when symptoms such as severe dementia and impaired motor function emerge. Behavioural problems disappear gradually as the patient loses motor control and experiments difficulty in swallowing and muscle spasticity. Finally, the patient falls into a vegetative state and usually dies during the second or the third decade of life (1).

Mild phenotype is characterized by a more gradual progression of the disease and an increase of longevity (10). The first phase starts approximately at the age of four and it shows a poor development and language delay. In the mild phenotype, the second stage is the slowest, compared with severe phenotype. Mild cognitive impairment can remain stable during adolescence or even adulthood before it progresses. Behavioural problems, similar to those present in severe phenotypes, also appear in patients suffering from mild phenotype, but they appear later and are easier to deal with. The third stage and death usually take place during the fourth and sixth decade of life. However, there are cases reported in the literature of survivors at the age of seventy. Having into account that early diagnosis in this group of population is especially difficult, it is not strange that patients suffering from mild phenotype are not diagnosed until adulthood.

Biochemical tests

Not all the laboratories are equipped with the facilities required to carry out the analytical tests of MPS III. The laboratory chosen shall be authorized and have experience with this kind of tests. As previously mentioned, MPS III is characterized by the impossibility to catabolize heparansulfate. Therefore, not only this molecule accumulates in the tissues, but is also excreted in excess through urine. The analysis of GAG in urine could detect the excess of this molecule, but it does not allow to distinguish between the different subtypes of MPS.

The analysis of GAG in urine is the first step in the biochemical diagnosis as it is unexpensive and non-invasive. Traditionally, both semiquantitative techniques (using cationic stainings, such as Berry test, Ames spot, etc.) and quantitative techniques (using spectrophotometric com-

pounds, such as dimethylmethylene blue, alcian blue, etc.) have been used. However, the former have a relatively high rate of false positive and negative results and have been set aside. In fact, some authors consider that these are obsolete tests (11). Therefore, quantitative techniques are preferred whilst semiquantitative techniques are not recommended as single screening test (see Table 3).

To determine the specific MPS subtype, all the samples with a high number of GAG will be analyzed by qualitative techniques. Recently, a technique based on liquid chromatography and tandem mass spectrometry has been proved efficient to determine the subtype of MPS with high specificity and sensitivity (12). Although the analysis of GAG in urine is simple, some factors must be considered. Firstly, patients with MPS III have a lower number of GAG in urine in comparison with other types of MPS. There may be a high number of false negatives. Therefore, a negative result in the urine analysis of GAG does not rule out the diagnosis of MPS III (3). Secondly, there may be false positives, especially when electrophoresis is used. This may happen if the urine sample is kept in a heparinized test tube, because the heparin migrates to the same position than heparan sulfate during the electrophoresis. After the analysis of GAG in urine, the enzyme activity tests are the gold standard to confirm the diagnosis and determine the subtype of MPS III. The enzyme activity can be measured in cultures of skin fibroblasts, leucocytes, plasma and serum and the four enzymes from each subtype can be analyzed (13). Absent or decreased activity in any of the enzymes involved in the catabolism of heparan sulfate lets the diagnosis of MPS III.
There is a great interest in determining the prognostic value of the residual enzyme activity with regards to the phenotype severity. However, it has been proved that the level of residual enzyme activity does not correlate with the disease phenotype (mild or severe) and shall not be used for such purpose (14).

Early diagnosis

It is clear that mucopolysaccharidosis type III means a diagnostic challenge, especially in early stages and in the absence of family history of the disease. The physician must examine the whole patient and deduce a metabolic disease from the set of signs and symptoms. During the first phase, the patients typically experience developmental and/or language delay, accompanied by specific signs and symptoms (see table 2). The diagnostic examination process (starting with the analysis of GAG in urine) is recommended with the sole presence of developmental delay and one of the specific physical features. The aim of this test is to avoid mistakes in diagnosis and unnecessary treatments that are, as mentioned above, quite frequent in this disease.

During the second phase, the developmental delay is accompanied by disturbed behaviour and sleep disorders. The lack of response to stimulating drugs for ADHD or to behavioural therapy is a key clue to diagnose the disease at this stage. Any of these neurocognitive signs, alone or combined with typical physical features of mucopolysaccharidosis type III, raise suspicion of the disease and lead to the determination of GAG in urine sample.

Prenatal diagnosis and genetic tests

Prenatal diagnosis can be performed in the chorionic villi and in the amniotic fluid. In the first case, the test can be carried out since 10-12 weeks of pregnancy, while the amniotic fluid test can be carried out since week 15-16. If the genotype of the index case is available, prenatal diagnosis can be carried out in the chorionic villi without cultures because DNA can be extracted directly. Then, the examination can be carried out at the beginning of the gestation. If the mutations from the index case are unknown, cultures from chorionic villi and amniotic fluid will be required.

Molecular genetic tests in the chorionic villi or in amniotic fluid cells are available in some centres for couples with family history of MPS III as prenatal diagnosis test in subsequent gesta-

tions. This is the only way to identify carriers of the disease.

Several mutations have been reported regarding all the 4 genes that cause the disease: 115 in sulfamidase (MPS IIIA), 134 in N-acetylglucosaminidase (MPS IIIB), 54 in acetyl-CoA-glucosamine-N-acetyltransferase (MPS IIIC) and 23 in N-acetylglucosamine-6-sulfate sulfatase (MPS IIID). Although several researchers have tried to correlate the genotype with the fenotype of each subtype of MPS III, no correlation has been found yet.

Referral to specialists and follow-up

Early diagnosis is key for patients with MPS III. If no screening test was carried out in the newborn, the pediatricians are the main actors involved as they see the children in early stages of MPS III. Once the diagnosis is established, the patient will be referred to the specialist on metabolic diseases, but the role of the pediatrician is key in the follow-up of the patient. During the follow-up, the patient will be referred to many other specialists, mainly cardiologists, neurologists, ophtalmologists, traumatologists, otolaryngologists, psychiatrists and pulmonologists. Furthermore, additional support measures such as physiotherapy, occupational therapy, speech therapy, audiology and behavioural therapy, among others, could be required.

Treatment options

Since there are no curative therapies, several treatments aimed to cure this disease are in development. Clinical trials on humans are being carried out with intrathecal enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). Besides, gene therapy and drug therapy with chaperons are being studied in animal models (15). The findings suggest that ideal results would be obtained when these therapies are applied before an extense neurological damage has occured. Hematopoietic stem cell transplant with bone marrow cells has been carried out. However, this treatment has not proved useful in the prevention of neurocognitive impairment even when carried out in early stages of the disesase, so it is not considered as a feasible treatment option. Despite this therapy failed to prevent neurocognitive impairment, experiments carried out on animals with umbilical cord blood stem cells have shown promising results (16).

The intrathecal administration of ERT aimed to reach the brain with an implantable device has shown promising results in animal models with MPS I and is currently being studied in patients with MPS I, II and IIIA, in phase I/II clinical trial (17).

Treatment of MPS IIIB with synthetic compounds of soy isoflavone genisteins on mice has shown potential, with reports showing complete correction of the mice behaviour. These extracts have been studied on humans in open trials, with some improvements of the gastrointestinal symptoms, skin texture and rate of infections. However, the effects on the cognitive funcion and global disability have been minimal (18).

Conclusions

Mucopolysaccharidosis type III is a hereditary metabolic disease that has a diverse way of appearing, and a progressive clinical course, characterized by a gradual neurocognitive decline, disturbed behaviour or notably characteristic physical expression. Currently, no curative therapy exists, but it is believed that an earlier establishment of therapies that had not been proved to be effective might become a remedial option. Thus, early examination and diagnosis are crucial to optimize therapeutic outcomes. Pediatricians play a key role in the identification of those patients showing a set of symptoms that corresponds with the profile of this metabolic disease. It is important to underline the difficulty in this process and the high frequency of false diagnosis. In fact, due to the delicacy of its physical features, children with mucopolysaccharidosis type III tend to be misdiagnosed with a wide variety of diseases such as language or idiopathic developmental disorder, ADHD or autism. Physicians must be careful then, and assess the whole patient considering the possibility of being a metabolic disease. The presence of delayed development or language added to any other physical feature re-

lated to the disease or disturbed behaviour must lead to an early examination (See Figure 1). If in doubt, the best procedure is diagnostic examination, because determination of GAG in urine is cheap and non-invasive, although it must be considered that a negative result does not rule out the disease. Enzyme activity must be tested in those patients with positive GAG determination test in urine and in those with a high probability of suffering from this disease, being able to establish the subtype of mucopolysaccharidosis through this technique. Molecular genetics tests and prenatal diagnosis can be offered to the families of patients suffering from mucopolysaccharidosis type III as to identify carriers and ease informed decisions by relatives. Once the diagnosis is made, patients must be referred to a metabolic disease specialist, but pediatricians and primary care physicians still play a key role directing the multidisciplinary teams.

Tabla 1

Subtipos de la MPS III, genética, clínica y porcentaje en España.

Subtipo de MPS III	Enzima alterada	Particularidades clínicas	Gen que codifica la enzima	Porcentaje de afectados
A	Heparán-N-sulfatasa	Es el subtipo más grave, con aparición más precoz y progresión más rápida de los síntomas, así como una supervivencia más baja.	17q25.3	62 %
B	α-N-acetilglucosamina	Heterogeneidad clínica	17q21.1	20 %
C	Acetil-CoA-α-glucosamin-acetiltransferasa	Gran heterogeneidad clínica	¿14q/21q?	18 %
D	N-acetil-glucosamina-6-sulfatasa	Gran heterogeneidad clínica.	12q14	0 %[a]

Nota. Los datos proceden de Delgadillo V, O'Callaghan M, Gort L, Coll MJ, Pineda M. Natural history of Sanfilippo syndrome in Spain. Orphanet Journal of Rare Diseases 2013, 8:189 doi: 10.1186/1750-1172-8-189.

Tabla 2

Fenotipos, estadios y manifestaciones principales asociadas de la MPS III.

Fenotipo	*Grave*	*Leve*
Presintomático	Sin síntomas	Sin síntomas
Inicio 1ª fase	1-3 años	4 años
Manifestaciones 1a fase	**Neurocognitivas:** ↓ Desarrollo cognitivo (lenguaje ++). **Somáticas:** Dismorfias faciales; hepatomegalia; esplenomegalia; infecciones de vía respiratoria alta e infecciones otológicas; enfermedad valvular; hernia umbilical e inguinal; diarrea.	↓ Desarrollo (lenguaje ++).
Inicio 2ª fase	3-4 años	Adolescencia
Manifestaciones 2ª fase	**Neurocognitivas:** Deterioro cognitivo progresivo y retraso mental; trastornos del sueño (insomnio, sonambulismo); alteraciones de conducta (hiperactividad, impulsividad, agresividad, agitación, ansiedad, autolesión, compulsión, desórdenes de tipo autista, deterioro del control motor, epilepsia). **Somáticas:** Pérdida auditiva; malformaciones ortopédicas (escoliosis, cifosis, lordosis lumbar, displasia de cadera, síndrome del túnel carpiano, dedos en gatillo, contracturas articulares).	Deterioro cognitivo leve. Alteraciones de conducta. Trastornos del sueño.
Inicio 3ª fase	Adolescencia	40-60 años
Manifestaciones 3ª fase	**Neurocognitivas:** Deterioro cognitivo progresivo y retraso mental profundo; déficit completo de lenguaje; cese de las alteraciones de conducta. **Somáticas:** Dificultad para tragar; espasticidad; epilepsia; dismorfias faciales; pérdida auditiva; malformaciones ortopédicas.	Demencia grave. Deterioro motor. Estado vegetativo. Fallecimiento.

Nota. Fuente: Adaptado de Wijburg FA, Wegrzyn G, Tylki-Szymanska A. Mucopolysaccharidosis type III (Sanfilippo syndrome) and misdiagnosis of idiopathic developmental delay, attention deficit/hyperactivity disorder or autism spectrum disorder. Acta Paediatr. 2013; 102(5): 462-470.

Tabla 3:

Técnicas para el análisis de GAG en orina

Tipo de técnica	**Nombre de la técnica**	**Sensibilidad**	**Especificidad**	**Valor pronóstico**	**Efectividad de la prueba**	**Otros**
Cuantitativa	Colorimetría con azul de dimetilmetileno. (DMB)	100 %	74.5 %	82.35 %	97.77 %	La técnica es simple y necesita una muestra de orina pequeña.
	Complejos ácido-azul alcián	100 %	88.46 %	25 %	88.88 %	Técnica algo más compleja que el DMB y, por ello, menos usada.
	Test de turbidez con cloruro de cetilpiridinio	99 %	55 %	15.9%	92 %	Técnica bastante primitiva. Debido a su baja especificidad y sensibilidad, su uso está desaconsejado.
Semicuantitativa	Test de Berry	93.6 %	53.9 %	0%	95 %	Simple y barato, pero desaconsejado para *screening*.
	Ames spot	65 %	71 %	0%	90 %	Desaconsejado para *screening*.

Nota. Fuente: Adaptado de Maceira Rozas MC, Atienza Merino G. Detección precoz de mucopolisacaridosis y oligosacaridosis en el período neonatal mediante cribado poblacional. Revisión sistemática. Madrid: Ministerio de Sanidad y Consumo. Avalia-t No 2006/08.

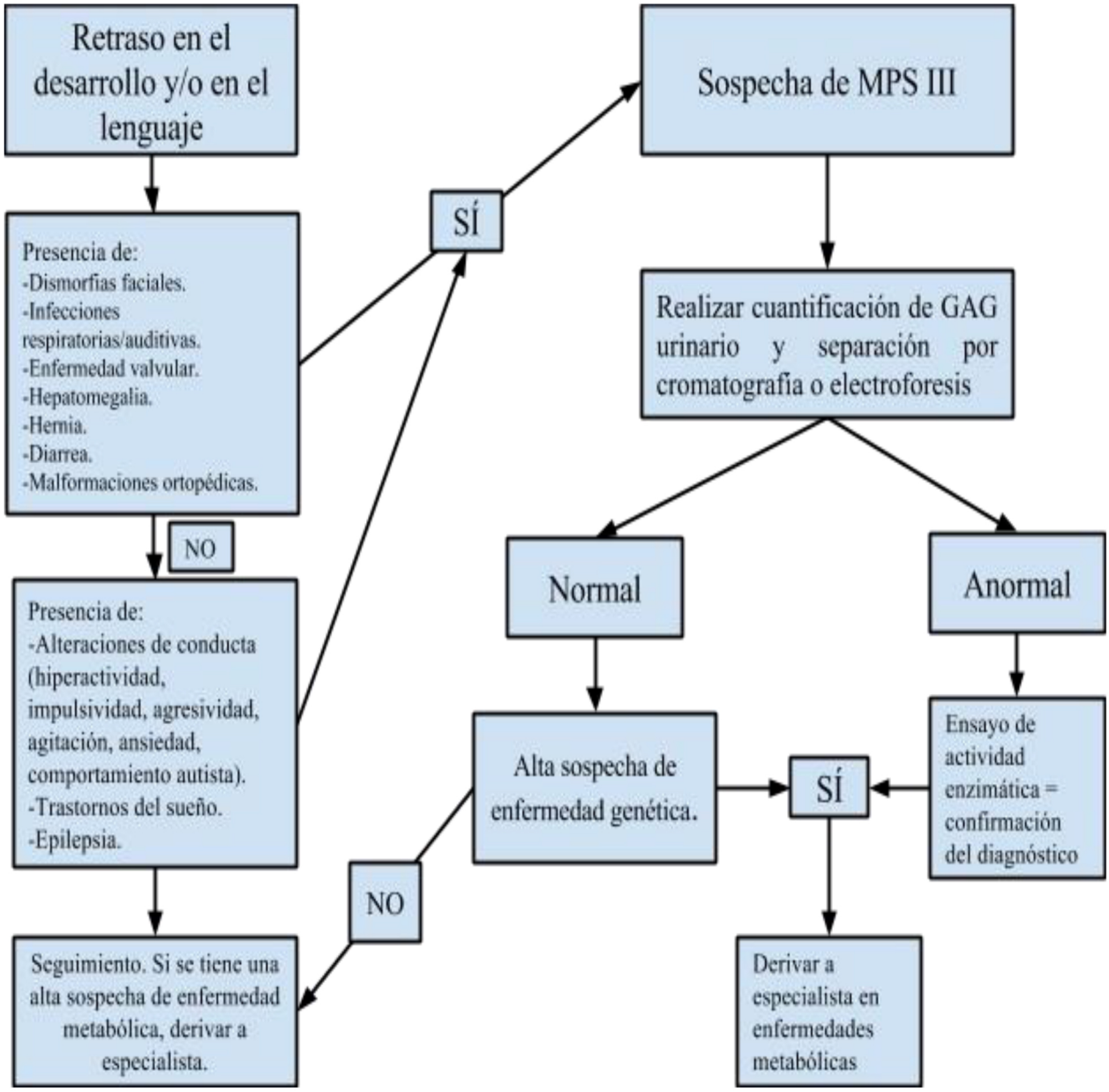

Figura 1. Diagnóstico Temprano de MPS III

Fuente: Adaptado de Wijburg FA, Wegrzyn G, Tylki-Szymanska A. Mucopolysaccharidosis type III (Sanfilippo syndrome) and misdiagnosis of idiopathic developmental delay, attention deficit/hyperactivity disorder or autism spectrum disorder. Acta Paediatr. 2013; 102(5): 462-470.

References

1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, editor. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill; 2001.
2. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA. 1999;281:249–54.
3. Wijburg FA, Wegrzyn G, Tylki-Szymanska A. Mucopolysaccharidosis type III (Sanfilippo syndrome) and misdiagnosis of idiopathic developmental delay, attention deficit/hyperactivity disorder or autism spectrum disorder. Acta Paediatr. 2013; 102(5): 462-470.
4. Delgadillo V, O'Callaghan M, Gort L, Coll MJ, Pineda M. Natural history of Sanfilippo syndrome in Spain. Orphanet Journal of Rare Diseases 2013, 8:189 doi: 10.1186/-1750-1172-8-189.
5. White KK, Karol LA, White DR, Hale S. Musculoskeletal manifestations of Sanfilippo syndrome (mucopolysaccharidosis type III). J Pediatr Orthop. 2011;31:594–8.
6. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, editor. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill; 2001.
7. Garbuzova-Davis S, Mirtyl S, Sallot SA, Hernandez-Ontiveros DG, Haller E, Sanberg PR. Blood-brain barrier impairment in MPS III patients. BMC Neurology 2013, 13:174
8. van de Kamp JJ, Niermeijer MF, von Figura K, Giesberts MA. Genetic heterogeneity and clinical variability in the Sanfilippo syndrome (types A, B, and C). Clin Genet. 1981;20:152–60. BMC Neurol. 2013 Nov 13;13:174
9. Mahon LV, Lomax M, Grant S, Cross E, Hare DJ, et al. (2014) Assessment of Sleep in Children with Mucopolysaccharidosis Type III. PLoS ONE 9(2): e84128. doi:10.1371/journal.pone.0084128
10. Moog U, van Mierlo I, van Schrojenstein Lantman-de Valk HM, Spaapen L, Maaskant MA, Curfs LM. Is Sanfilippo type B in your mind when you see adults with mental retardation and behavioral problems? Am J Med Genet C Semin Med Genet.2007;-145C:293–301.
11. Bodamer OA, Giugliani R, Wood T. The laboratory diagnosis of mucopolysaccharidosis III (Sanfilippo syndrome): A changing landscape. Mol Genet Metab. 2014 September - October;113(1-2):34-41
12. Chuang CK, Lin HY, Wang TJ, Tsai CC, Liu HL, Lin SP. A modified liquid chromatography/tandem mass spectrometry method for predominant disaccharide units of urinary glycosaminoglycans in patients with mucopolysaccharidoses. Orphanet J Rare Dis. 2014 Sep 2;9:135.
13. Marsh J, Fensom AH. 4-Methylumbelliferyl alpha-N-acetylglucosaminidase activity for diagnosis of Sanfilippo B disease. Clin Genet. 1985;27:258–62.
14. Piotrowska E, Jakobkiewicz-Banecka J, Tylki-Szymanska A, Czartoryska B, Wegrzyn A, Wegrzyn G. Correlation between severity of mucopolysaccharidoses and combination of the residual enzyme activity and efficiency of glycosaminoglycan synthesis. Acta Paediatr. 2009;98:743–9.
15. de Ruijter J, Valstar MJ, Wijburg FA. Mucopolysaccharidosis type III (Sanfilippo syndrome): emerging treatment strategies. Curr Pharm Biotechnol. 2011;12:923–30.
16. Welling L, Marchal JP, van Hasselt P, van der Ploeg AT, Wijburg FA, Boelens JJ. Early Umbilical Cord Blood-Derived Stem Cell Transplantation Does Not Prevent Neurological Deterioration in Mucopolysaccharidosis Type III. JIMD Rep. 2014 Sep 26.
17. Dickson PI, Chen AH. Intrathecal enzyme replacement therapy for mucopolysaccharidosis I: translating success in animal models to patients. Curr Pharm Biotechnol. 2011;12:946–55.
18. Piotrowska E, Jakobkiewicz-Banecka J, Maryniak A, Tylki-Szymanska A, Puk E, Liberek A, et al. Two-year follow-up of Sanfilippo disease patients treated with a genistein-rich isoflavone extract: assessment of effects on cognitive functions and

general status of patients. Med Sci Monit.
2011;17:CR196–202