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Diagnosis and follow-up of patients with Hunter syndrome in Spain

A Delphi consensus

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Abstract

Hunter syndrome or mucopolysaccharidosis type II (MPSII) is a progressive multisystem X-linked lysosomal storage disease caused by mutations in the *IDS* gene that shows a wide spectrum of clinical symptoms and severity. Idursulfase, a specific enzyme replacement therapy (ERT) for MPSII, has been available since 2007. ERT, along with symptomatic management of patients, is fundamental for improving patient prognosis and quality of life. The aims of this study were to investigate whether Spanish pediatricians who are experts in managing the disease agreed with current international guidelines regarding MPSII patient diagnosis and follow-up; and to reach a consensus regarding which items are essential for the diagnosis, follow-up, and treatment of these patients in Spain.

An advisory panel of 5 experts from the Hunter Spanish Working Group reviewed key studies, developed a questionnaire based on a modified Delphi method, sent the questionnaire to selected experts, and reviewed the responses. The final questionnaire had 83 items in the following categories: diagnosis, ERT considerations after diagnosis, Periodic assessments, and ERT considerations during follow-up. A total of 85 experts were invited to participate; 28 (35%) responded and showed a strong consensus for most items. The advisory panel decided not to perform a second Delphi round. There was strong agreement (>3.1 median value; range, 1 to 4) for 43/56 items in Diagnosis, for 4/6 items in "ERT considerations after diagnosis," for 6/16 items in "Periodic assessments," and for 3/5 items in "ERT considerations during follow-up." Most responses were in agreement with international guidelines, and controversial items were discussed by the advisory panel. Based on the results, on the key studies, and on clinical experience and opinions, the panel developed and scheduled recommendations for the diagnosis and follow-up of patients with MPSII.

An expert 5-person panel oversaw a Delphi survey of 28 pediatricians and reached a consensus on recommendations for the diagnosis and follow-up of MPSII patients. This document will help guide clinicians involved in the diagnosis, management, and treatment of MPSII.

Abbreviations: 6MWT = 6-minute walk test, BP = blood pressure, CHAQ = Childhood Health Assessment Questionnaire, CHQ = Childhood Health Questionnaire, CSF = cerebrospinal fluid, CT = computed tomography, CTS = carpal tunnel syndrome, ECC = echocardiogram, ECG = electrocardiogram, EEG = electroencephalography, EMG = electromyography, ENT = ear, nose, and throat, ERT = enzyme replacement therapy, GAG = glycosaminoglycans, HS-FOCUS = Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale, HUI = Health Utilities Study, MPSII = mucopolysaccharidosis type II, MRI = magnetic resonance imaging, PedsQL = Pediatric Quality of Life inventory, QoL = quality of life, US = ultrasound, XR = x-ray (radiography).

Keywords: Delphi, diagnosis, Hunter syndrome, idursulfase, management, mucopolysaccharidosis type II

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1. Introduction

Hunter syndrome, also called mucopolysaccharidosis type II (MPSII), is a rare X-linked lysosomal storage disease. Mutations in the *IDS* gene cause a deficiency in the iduronate 2-sulfatase enzyme, which reduces glycosaminoglycan (GAG) catabolism in lysosomes. Consequently, there is an accumulation of dermatan sulfate and heparan sulfate in the cells of many tissues and organs, and it is this accumulation of GAGs that is responsible for the clinical phenotype of the disease.[1]

The estimated incidence of MPSII in live male newborns is 1:162,000.[2] However, the incidence varies widely in different countries and regions, ranging from 1:49,000 to 1:526,000.[3] Data from the Hunter Outcomes Survey (HOS) Registry show just 45 diagnosed patients in Spain. Since it is an X-linked disorder, there are very few female patients, although some heterozygous female patients develop signs and symptoms of the disease.[4,5]

MPSII is a variable, progressive, and multisystem condition. Traditionally, it has been classified as mild or severe, with the severe subtype characterized by central nervous system (CNS) involvement and poorer survival. However, MPSII is currently described as a continuum of phenotypes that range from attenuated to severe disease.[1,4] Patients may present with facial dysmorphism, hepatosplenomegaly, hernias, musculoskeletal abnormalities, respiratory dysfunction, cardiac abnormalities, carpal tunnel syndrome, CNS involvement, impaired intellect, behavioral disorders, and visual and hearing problems.[1,6] Because of the wide spectrum of clinical presentation and severity of the disease, MPSII management is complex and requires a multidisciplinary approach.[3,4,7] Notably, specific enzyme replacement therapy (ERT) using idursulfase (Elaprase, Shire) became available in 2007.[8] ERT has changed the prognosis and evolution of the disease[9–21] and strengthened the importance of early diagnosis.[1,22]

There are several guidelines for the diagnosis and management of MPSII .[2,5,23,24] The aims of this study were to investigate whether Spanish pediatricians who are experts in managing the disease agreed with current international guidelines regarding MPSII patient diagnosis and follow-up; and to reach a consensus regarding which items are essential for the diagnosis and follow-up of these patients in Spain.

2. Methods

A modified Delphi method was used to obtain expert consensus on the diagnosis and follow-up of MPSII patients in clinical practice in Spain. The Delphi method is a process to reach consensus using sequential questionnaires that are answered anonymously by an expert panel.[25] Among other uses, the Delphi method has been utilized to develop clinical guidelines.[26]

The advisory panel included 5 members of the Hunter Spanish Working Group, a Spanish multidisciplinary team with physicians who are experts in the diagnosis and management of MPSII patients. First, we reviewed a bibliography to determine which topics merited discussion. The Hunter Spanish Working Group published clinical practice guidelines for the management of MPSII in 2013,[3] so the key variables were determined based on the references in that manuscript as well as on studies that were published later. Afterward, we had a face-to-face meeting to choose the questionnaire items and to review the survey online.

Spanish pediatricians with present or past experience with MPSII were invited to participate in the study. The selection criteria were as follows: knowledge of MPSII (publications and participation in scientific meetings), clinical experience (working at a specialized clinic at a reference center), and level of scientific influence. The final questionnaire had 83 items divided into 4 categories: diagnosis, ERT considerations after diagnosis, periodic assessments, and ERT considerations during follow-up. The items were worded to establish the recommendation grade, with 4 possible answers to the "center-stage effect": 4 ("Strongly agree"), 3 ("Quite agree"), 2 ("Somewhat agree"), and 1 ("Totally disagree").

Table 1

Equivalence between the median scores and recommendation grades.

Median	Recommendation grade
4 (strongly agree)	Highly recommended/agreed minimal dataset
3 (quite agree)/2 (somewhat agree)	Quite/somewhat recommended/to be performed at excellence centers
1 (totally disagree)	Not recommended

The survey was released using a web-based platform that was specifically designed for the study. Weekly reminder emails were sent to 85 selected experts in April and May of 2015. After the response deadline, the medians and means of the response scores were analyzed. The median scores were calculated in order to cancel out the possible influence of extreme and divergent answers. The equivalence between the median scores and the recommendation grades were determined (Table 1).

The advisory panel members reviewed the responses and then held a face-to-face meeting to discuss the results and, where appropriate, to reach a consensus on the recommendations. A second Delphi round was planned in case the responses in the first round were not conclusive.

3. Results

3.1. First round results

Of the 85 experts that were invited to participate in the survey, 28 (35%) completed the questionnaire. The first round results are shown in Table 2.

3.2. Review of the results

The advisory panel members reviewed the first round results and found a strong consensus for most of the answers (43 of 56 items in "Diagnosis," 4 of 6 items in "ERT considerations after diagnosis," 6 of 16 items in "Periodic assessments," and 3 of 5 items in "ERT considerations during follow-up"). Therefore, there was no need for a second Delphi round.

However, for some items, there was disagreement between the survey results and the advisory panel members that merited further analysis. These items were considered controversial. The decisions about whether to include these items in the final recommendations were based on specific literature searches and on our own experience and opinions. For clarification, these items needed further explanations.

3.2.1. Controversial items related to diagnosis.

- Item 20. Lipid profile (Median response: Quite agree). This was a verification/validation item. The lipid profile may be performed, but it is not required.
- Item 30. Intraocular pressure (Quite agree). The measurement of intraocular pressure is not essential, but in some cases in

Table 2

First round questionnaire results.

Item	Median	Mean
Diagnosis		
General		
1. First assessment by a Hunter syndrome expert	Strongly agree	3.6
2. Family history	Strongly agree	3.8
3. Personal history	Strongly agree	3.9
4. Recurrent infections	Strongly agree	3.7
5. Prior surgeries	Strongly agree	3.8
6. Orthopedic problems	Strongly agree	3.9
7. Audition problems	Strongly agree	4.0
8. Psychomotor developmental milestones	Strongly agree	4.0
Physical examination		
9. Weight	Strongly agree	3.8
10. Height	Strongly agree	3.9
11. Head circumference	Strongly agree	3.7
12. BP	Strongly agree	3.4
13. Dysmorphism	Strongly agree	4.0
14. Hernias	Strongly agree	3.9
15. Hepatosplenomegaly	Strongly agree	4.0
16. Skeletal deformities	Strongly agree	4.0
17. Joint range of motion	Strongly agree	3.6
Laboratory tests		
18. Blood count	Strongly agree	3.6
19. Metabolic panel	Strongly agree	3.6
20. Lipid profile	Quite agree	3.2
21. Quantitative analysis of urinary GAG	Strongly agree	4.0
22. Qualitative analysis of urinary GAG	Strongly agree	3.9
23. I2S enzyme activity	Strongly agree	3.9
24. Genetic study	Strongly agree	4.0
ENT manifestations		
25. Assessment by an ENT specialist	Strongly agree	3.9
26. Audition assessment (evoked potentials or audiometry)	Strongly agree	3.9
Ocular manifestations		
27. Visual acuity	Strongly agree	3.8
28. Fundus evaluation	Strongly agree	3.6
29. Slit lamp examination	Strongly agree	3.5
30. Intraocular pressure	Quite agree	3.3
Respiratory system		
31. Oxygen saturation	Quite agree	3.2
32. Respiratory function by spirometry	Strongly agree	3.8
33. Functional status using the 6MWT	Strongly agree	3.5
34. Sleep-related respiratory problems using a standard questionnaire	Strongly agree	3.4
35. Polysomnography	Strongly agree	3.3
Cardiovascular system		
36. ECG	Strongly agree	3.6
37. Echocardiogram	Strongly agree	3.8
38. Holter	Somewhat agree	2.5
Digestive system/abdominal		
39. Volumetric measurement of liver/spleen by US	Strongly agree	3.6
40. Volumetric measurement of liver/spleen by CT	Somewhat agree	1.9
41. Volumetric measurement of liver/spleen by MRI	Quite agree	2.7
Musculoskeletal system and joints		
42. Spine XR	Strongly agree	3.7
43. Hip XR	Strongly agree	3.7
44. Wrist XR	Strongly agree	3.5
45. Bone survey	Strongly agree	3.2
46. Spinal MRI	Quite agree	3.2
Neurological system		
47. EEG	Quite agree	2.4
48. Brain CT	Somewhat agree	1.8
49. Brain MRI	Strongly agree	3.4
50. EMG	Somewhat agree	2.4

(*continued*)

Table 2

(continued).

Item	Median	Mean
51. Electroneurography	Somewhat agree	2.5
52. Lumbar puncture with measurement of CSF pressure	Totally disagree	1.4
53. Neuropsychological assessment	Strongly agree	3.8
Functionality. Activities of daily living		
54. Functionality scale	Strongly agree	3.7
Quality of life		
55. QoL measurement by a patient- and parents/caregivers-completed disease-specific questionnaire	Strongly agree	3.7
56. QoL measurement by a patient- and parents/caregivers-completed generic pediatric questionnaire	Quite agree	3.1
ERT considerations after diagnosis		
1. Early ERT can change the natural history of the disease	Strongly agree	3.7
2. Provide oral and written ERT information to the patient and/or parents or caregivers regarding consequences, prospects and discontinuation causes	Strongly agree	4.0
3. Initiate ERT in patients with mild disease	Strongly agree	3.6
4. Initiate ERT in patients with severe phenotype	Quite agree	3.0
5. Initiate ERT in patients with very severe neurological disease	Totally disagree	1.5
6. Genetic counselling and screening of female relatives at risk of being carriers	Strongly agree	3.9
Periodic assessments		
1. Periodic follow-up visits have to be advised by an expert in Hunter syndrome	Strongly agree	3.8
2. Complete assessment, including complementary testing, every 6 months during the first 2 years after the diagnosis	Strongly agree	3.4
3. Complete assessment, including complementary tests, every 12 months during the first 2 years after the diagnosis	Quite agree	2.8
4. Every 6 months, only clinical assessment (only case history and physical exam)	Somewhat agree	2.3
5. Further testing according to clinical signs and symptoms	Totally disagree	1.8
6. Periodic further testing according to patient age, independent of disease severity	Quite agree	2.5
7. Periodic further testing according to disease severity	Quite agree	2.9
8. Periodic cardiac exam	Strongly agree	3.6
9. Periodic 6MWT and respiratory assessment in collaborator patients	Strongly agree	3.4
11. Periodic cervical MRI	Quite agree	2.6
12. Periodic electroneurography	Somewhat agree	2.2
13. Periodic neuropsychological assessment	Strongly agree	3.5
14. Periodic assessment of functionality and QoL scales	Strongly agree	3.6
15. Periodic measurement of antibody titer	Quite agree	2.6
ERT considerations during follow-up		
1. Discontinue ERT in patients with mild disease	Totally disagree	1.5
2. Discontinue ERT in patients with severe disease	Somewhat agree	2.0
3. Periodic ERT reassessment in patients with severe disease	Strongly agree	3.8
4. Adult reference centers to continue patient care	Strongly agree	4.0
5. Regional/national expert committees to assess indications and follow-up of ERT	Strongly agree	3.9

6MWT = 6-minute walk test, BP = blood pressure, CSF = cerebrospinal fluid, CT = computed tomography, EEG = electroencephalography, EMG = electromyography, ENT = ear, nose and throat, ERT = enzyme replacement therapy, GAG = glycosaminoglycan, MRI = magnetic resonance imaging, QoL = quality of life, US = ultrasound, XR = x-ray (radiography).

which it seems of clinical interest, it could be performed (if possible in the hospital). In such patients, evaluation of the central corneal thickness is recommended to adequately assess intraocular pressure and possibly coexistent glaucoma. However, glaucoma is rare in MPSII.[27,28]

- Item 31. Oxygen saturation (Quite agree). In uncooperative patients, it is easier to determine this than to have the patient complete the 6-minute walk test (6MWT).
- Item 38. Holter (Somewhat agree). This is another verification/validation item that is not essential in MPSII patients unless it is indicated after a cardiologist evaluation using electrocardiogram (ECG) and echocardiogram (ECC).
- Item 41. Magnetic resonance imaging (MRI) volumetric measurement of the liver and spleen (Quite agree). Abdominal echography is usually performed to measure the liver and spleen volume. However, abdominal MRI can also be performed if anesthesia is not needed or at the same time as a spine MRI.[3]
- Item 46. Spine MRI (Quite agree). MPSII patients show a wide spectrum of brain and spine abnormalities that should be thoroughly assessed. Moreover, white matter atrophy, hydrocephalus, and spinal stenosis might be markers of disease severity for evaluating treatment efficacy.[29] In addition, abnormalities in the cervical spine MRI are common in MPSII, although there are currently no clear correlations between MRI findings and patient phenotype.[28]
- Item 47. Electroencephalography (EEG) (Quite agree). MPSII patients may suffer from seizures during disease evolution.[31] Therefore, it would be useful to get a baseline EEG to compare with later EEGs.
- Item 48. Brain computed tomography (CT) (Somewhat agree). Spanish guidelines recommend brain CT as needed during patient follow-up.[3,5] However, this test should not be performed in children except in emergency situations.
- Item 50. Electromyography (EMG) (Somewhat agree) and 51. Electroneurogram (Somewhat agree). EMG records muscular electric activity and does not provide any useful data in MPSII. In addition, it is a painful test that requires the insertion of needle electrodes. In contrast, electroneurography is important in the diagnosis and follow-up of patients because carpal tunnel syndrome (CTS) is common in MPSII patients.[1,7,24] However, the typical symptoms of median nerve compression are rare in children with other types of mucopolysaccharidoses and more common in those with MPSII.[32,33] These symptoms have an insidious onset and can be hidden by skeletal dysplasia and joint stiffness, thereby delaying the CTS diagnosis. Cognitive impairment may contribute to the lack of a diagnosis.[34] Moreover, CTS can cause behavioral problems in patients with MPSII.[24] Therefore, electroneurography is recommended in patients with MPSII[23] at age 3 to 4 years and every 1 to 2 years thereafter to exclude CTS. Notably, previous studies have reported that all MPSII patients over 2 years old are affected with CTS, mainly pulp atrophy and thenar eminence, thumb weakness, and decreased sweating; less often, there is an alteration in surface sensitivity and trophic changes.[7,24,32] As the compression progresses, there is a functional deficit in thumb functionality that can be very disabling in children older than 3 to 4 years old, depending on its severity. Item 56. Quality of life (QoL) measurement by a patient- and parent/caregiver-completed generic pediatric questionnaire (Quite agree). Several generic questionnaires have been used in MPSII patients and parents/caregivers: the Pediatric Quality of Life Inventory (PedsQL),[35] the Childhood Health Assessment Questionnaire (CHAQ), the Childhood Health Questionnaire (CHQ), and Health Utilities Index (HUI),[36] and the KIDSCREEN questionnaire.[37] However, there is also a patient- and parent/caregiver-completed disease-specific instrument, the Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale (HS-FOCUS) Questionnaire.[38] The shortened version has 6 domains (walking/standing, grip/reach, school/work, activities, breathing, and overall function score) and 18 items (patient) or 21 items (parents).[36,38]

3.2.2. Controversial items related to periodic assessments.

- Item 3. Complete assessment, including complementary tests, every 12 months during the first 2 years after the diagnosis (Quite agree). Published guidelines do not recommend complete assessment every 12 months during the first 2 years.[2–5]
- Item 4. Every 6 months, only clinical assessment (only case history and physical exam) (Somewhat agree). The advisory panel concluded that clinical assessment alone is inadequate.
- Item 5. Further testing according to clinical signs and symptoms (Totally disagree). This item was rejected because of its lack of specificity.
- Item 6. Periodic further testing according to patient age, independent of disease severity (Quite agree). Several manifestations of MPSII usually appear after age 5 years, including CTS, cardiac valve involvement, retinal dysfunction, respiratory failure, hydrocephalus, seizures, and spinal cord compression.[3,5] Therefore, there is a series of tests that should be performed in all patients who are at least 5 years old.
- Item 7. Further testing according to disease severity (Quite agree). Further testing may be needed for some conditions, such as chest radiography and/or bronchoscopy for pulmonary problems or polysomnography if apnea occurs.[3] In case of rapid progression, more frequent assessments are recommended.[2]
- Item 10. Periodic polysomnography (Quite agree). Obstructive sleep apnea and impaired gas exchange during sleep are common in patients with MPSII.[39] Polysomnography should be performed at baseline and should be repeated in case of sleep apnea or nocturnal snoring.[3]
- Item 11. Periodic cervical MRI (Quite agree). Abnormalities on the cervical spine MRI are common in MPSII.[30]
- Item 12. Periodic electroneurography (Somewhat agree). As noted above, electroneurography helps detect CTS.
- Item 15. Periodic measurement of antibody titer (Quite agree). The advisory panel agreed that periodic measurements of serum IgG anti-idursulfase antibodies could be useful in the future.
- Item 16. Periodic GAG measurement (Quite agree). ERT reduces urine GAG excretion, so this should be monitored.[4,24]

3.3. Recommendations for the diagnosis and follow-up of patients with MPSII

A series of recommendations for the diagnosis and follow-up of patients with MPSII was developed based on the results of this Delphi survey, on the bibliographical review, and on the clinical experience and opinions of the advisory panel (Table 3). An MPSII expert should be involved both at the first assessment and at the periodic follow-up visits.

Table 3

Recommendations for the diagnosis and follow-up of patients with Hunter syndrome.

	Schedule				
Recommendation	**Diagnosis**	**Before every therapy session**	**Every 6 months during the first 2 years, then every 12 months**	**Every 12 months**	**As needed according to patient evolution**
General					
Family history	X				
Personal history	X		X		
Recurrent infections	X		X		
Prior surgeries	X				
Orthopedic problems	X		X		
Auditory problems	X		X		
Psychomotor developmental milestones	X		X		
Physical examination					
Weight	X	X	X		
Height	X		X		
Head circumference	X		X		
BP	X	X	X		
Heart rate	X	X	X		
Dysmorphism	X	X	X		
Hernias	X	X	X		
Hepatosplenomegaly	X		X		
Skeletal deformities	X		X		
Joint range of motion	X		X		
Laboratory tests					
Complete blood count	X		X		
Metabolic panel	X		X		
Quantitative analysis of urinary GAG	X		X		
Qualitative analysis of urinary GAG	X		X		
I2S enzyme activity	X		X		
Genetic analysis	X				
Anti-idursulfase antibodies			X		
ENT manifestations					
Assessment by an ENT specialist	X				
Auditory assessment (evoked potentials or audiometry)	X				
Ocular manifestations					
Visual acuity	X		X		
Fundus evaluation	X		X		
Slit lamp exam	X		X		
Respiratory system					
Oxygen saturation	X	X	X		X
Assessment of respiratory function by spirometry	X		X		X
Assessment of functional status by means of 6MWT	X		X		X
Assessment of sleep-related respiratory problems using a standard questionnaire	X		X		
Polysomnography	X				
Cardiovascular system					
ECG	X				
Echocardiogram	X				
Digestive system/abdominal					
Volumetric measurement of liver/spleen by US	X		X		
Volumetric measurement of liver/spleen by RMI	?		?		
Musculoskeletal system and joints					
Spine XR	X		X		
Hip XR	X		X		
Wrist XR	X		X		
Bone assessment	X		X		
Spinal MRI	X		X		
Neurological system					
EEG	X				X
Brain CT					
Brain MRI	X			X	
Electroneurography	X			X*	

(*continued*)

Table 3

(continued).

Recommendation	Schedule				
	Diagnosis	Before every therapy session	Every 6 months during the first 2 years, then every 12 months	Every 12 months	As needed according to patient evolution
Neuropsychological assessment	X		X		
Functionality. Activities of daily living					
Functionality scale	X			X	
Quality of life					
HS-FOCUS	X			X	
PERIODIC ASSESSMENTS					
1. Periodic follow-up visits must be supervised by a Hunter specialist	Strongly agree				
2. Complete assessment, including complementary testing, every 6 months for the first 2 years after the diagnosis	Strongly agree				
3. Complete assessment, including complementary tests, every 12 months for the first 2 years after the diagnosis	Quite agree				
5. Further testing according to clinical signs and symptoms	Totally disagree				
6. Periodic complementary tests according to patient age, independent of disease severity	Quite agree				
7. Periodic additional testing according to disease severity	Quite agree				
8. Periodic cardiac exam	Strongly agree				
9. Periodic 6MWT and respiratory assessment in cooperative patients	Strongly agree				
10. Periodic polysomnography	Quite agree				
11. Periodic cervical MRI	Quite agree				
12. Periodic electroneurogram	Somewhat agree				
13. Periodic neuropsychological assessment	Strongly agree				
14. Periodic assessment of functionality and QoL scales	Strongly agree				
15. Periodic measurement of antibody titer	Quite agree				
16. Periodic GAG measurements	Quite agree				

6MWT = 6-minute walk test, CSF = cerebrospinal fluid, CT = computed tomography, EEG = electroencephalography, EMG = electromyography, ENT = ear, nose, and throat, ERT = enzyme replacement therapy, GAG = glycosaminoglycan, MRI = magnetic resonance imaging, QoL = quality of life, XR = x-ray (radiography).

* Every 1–2 years in children ≥4–5 years with attenuated disease.

3.4. Recommendations for ERT

Recommendations regarding ERT were developed based on the results of this study.

3.4.1. After diagnosis.

- Early ERT can change the course of the disease.
- Oral and written information about ERT should be provided to the patient and/or to parents or caregivers regarding the consequences of ERT therapy, the possible effects, and situations in which it should be discontinued.
- Initiate ERT in patients with mild disease.
- Initiate ERT in patients with severe phenotype.
- Do not initiate ERT in patients with very severe neurological disease since ERT will not improve their disease state.
- Provide genetic counselling and screening to female relatives of patients who are at risk of being carriers.

3.4.2. During follow-up.

- Do not discontinue ERT in patients with mild disease.
- ERT should be reassessed periodically in patients with severe disease.
- Adult reference centers should continue patient care.
- Regional/national expert committees should assess ERT indications and follow-up on the use of ERT.

4. Discussion

This is the first Delphi study carried out with Spanish pediatricians with experience in MPSII patient diagnosis and/or management of such pediatricians.

One limitation of this study was due to the organization of the Spanish National Health System and the absence of reference centers in Spain. However, during the course of this research and despite the decentralization of patients throughout Spain, we observed little disagreement between international guidelines for the diagnosis and follow-up of patients with MPSII and the opinions and clinical practices of clinicians in Spain.

As the clinical manifestations of MPSII affect multiple systems,[3,16,24], it is important to routinely assess various affected organs and systems, and each specialist should be included in the multidisciplinary team and should oversee continuing evaluations once a clinical problem is identified. Accordingly, the recommendations for the diagnosis and follow-up of patients with MPSII described here include the involvement of an expert in MPSII both at the first assessment and at the periodic follow-up visits, in order to provide advice.

Based on the results of Delphi survey, the bibliographical review, and the clinical experience and opinions of the advisory panel, a consensus was reached and a series of recommendations for the diagnosis and follow-up of patients with MPSII were developed. In terms of the controversial items related to diagnosis, it is notable that brain CT is not recommended in children, except in emergency situations, due to the difficulties associated with anesthesia. Also, experience with MPSII patients has shown that electroneurography is important for the diagnosis and follow-up of patients with this syndrome because CTS is common and very disabling in MPSII patients 3 to 4 years old or older.[1,7,23,24] This type of recommendation might be known by experts but not by all pediatricians.

The controversy regarding periodic assessments is based on the classification of patients by age and disease severity. Several manifestations of MPSII typically appear after age 5.[3] The multidisciplinary team should consider age, the disease severity and complications, which may vary not only between phenotypes but also within members of the same family,[40] in order to decide which tests should be performed.

There were no controversial issues regarding ERT initiation/cessation in MPSII patients. They were in agreement with the recommendations of Muenzer et al[41] and with other MPSII guidelines, which note that an improvement in quality of life as perceived by the family of a patient with severe disease should be considered a benefit of ERT treatment.[24] Moreover, the expert panel noted that the benefits of early treatment with ERT have been clearly demonstrated by HOS data[12,13] as well as by studies of siblings who were diagnosed and treated at different ages. This highlights the importance of genetic counselling and prenatal diagnosis.[42] Moreover, this consensus reflects the fact that the course of MPSII has been changed by ERT, and adult reference centers should be identified that can provide continued patient care. Supporting this idea, a series of recommendations were recently published for the best clinical management of the transitions of care of patients with inborn errors of metabolism.[43]

In conclusion, this study illustrates the usefulness of a modified Delphi method applied to clinical guidelines and provides extended recommendations for the diagnosis, management, and treatment of MPSII patients. These might be useful not only to pediatricians but also to other clinicians that are involved in the management of these patients.

Author contributions

LGGS was the coordinator of the expert panel. All authors reviewed the bibliography, developed the questionnaire, selected the experts, and reviewed the results. All authors edited, reviewed, and critically revised the manuscript and approved the final version.

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