



Experiences of parents and patients with the timing of Mucopolysaccharidosis type I (MPS I) diagnoses and its relevance to the ethical debate on newborn screening

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ABSTRACT

Introduction: Newborn screening (NBS) techniques have been developed for several lysosomal storage disorders (LSDs), including Mucopolysaccharidosis type I (MPS I). MPS I is an LSD with a wide phenotypic spectrum that ranges from the severe Hurler phenotype to the attenuated Scheie phenotype. To improve the ethical discussion about NBS for MPS I, we performed an interview study to explore the experiences of MPS I patients and their parents with the timings of their diagnoses.

Methods: We used a qualitative research approach consisting of 17 interviews with the parents of patients with all MPS I phenotypes and with patients with attenuated forms of MPS I. The interviews were audio-recorded, transcribed and subsequently analyzed to identify the main themes identified by the participants.

Results: Five important themes, focusing on the experienced disadvantages of delayed diagnosis and the advantages and disadvantages of a hypothetical earlier diagnosis, were identified in our group of participants: 1) delayed diagnosis causing parental frustration, 2) delayed diagnosis causing patient frustration, 3) early diagnosis enabling reproductive decision-making, 4) early diagnosis enabling focusing on the diagnosis, and 5) early diagnosis enabling timely initiation of treatment. There was a remarkable similarity in the experiences with timing of diagnosis between parents of patients with the severe and the attenuated forms.

Conclusion: This was the first study to explore the personal experiences of MPS I patients and their parents with diagnostic timing. Our study identified five important themes that are highly relevant to the ethical discussion on expanding NBS programs for MPS I.

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1. Introduction

In this era of expanding newborn screening (NBS) programs, lysosomal storage disorders (LSDs) have recently become attractive candidates for inclusion in screening panels because diagnostic and therapeutic options have significantly improved in recent years. Indeed, NBS has already been introduced for Fabry and Pompe disease in Taiwan and Krabbe disease in New York State (US). In addition, pilot programs for various LSDs, including Fabry, Pompe and Gaucher diseases and Niemann–Pick disease types A and B, have recently begun in Austria, Italy and several US states [1]. It is certain that LSDs will be introduced into more NBS programs worldwide in the near future.

Mucopolysaccharidosis (MPS) I, the subject of this study, is an attractive candidate for expanded NBS programs; it was recently designated by the US Advisory Committee on Heritable Disorders of Newborns and Children for an independent, evidence-based review to

assess the appropriateness of adding MPS I to the recommended uniform screening panel in the US. MPS I is a rare autosomal recessive LSD caused by a deficiency of the lysosomal hydrolase α -L-iduronidase (IDUA, EC 3.2.1.76) [2]. Its incidence has been estimated at 1:100,000 live births in the Netherlands, but this varies between regions; the highest reported number has been for Ireland (1:26,000) [3,4]. Its progressive signs and symptoms are the result of continuous accumulation of the glycosaminoglycans (GAGs) heparan sulfate and dermatan sulfate throughout the body, which leads to organ dysfunction. The MPS I phenotype is recognized as a continuous spectrum that ranges from severe (the 'Hurler' phenotype, MPS I-H) to more attenuated (the 'Hurler–Scheie' and 'Scheie' phenotypes, MPS I-H/S and MPS I-S). MPS I-H patients have an early-onset and rapidly progressive disease that involves the central nervous system (CNS) and leads to progressive neurodegeneration. If left untreated, MPS I-H patients die during the first two decades of life [2,5,6]. Hematopoietic stem cell transplantation (HSCT), which can preserve cognitive functions and ameliorate several of the somatic symptoms, is the treatment of choice for this group of patients. Because of the invariably progressive nature of the CNS disease, however, HSCT should be initiated at an early stage of the disease, preferably before the onset of cognitive impairment. Moreover, the HSCT

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success rate increases when the transplantation is performed at a younger age [7,8]. The patients with the more attenuated (MPS I-H/S and MPS I-S) phenotypes have a widely variable but generally much slower disease progression. Enzyme replacement therapy (ERT) is the treatment of choice for MPS I-H/S and MPS I-S patients [6,7]. The recombinant enzyme laronidase (Aldurazyme®) has been shown to be safe and to significantly ameliorate the somatic symptoms [9–13]. The optimal age for ERT initiation has not been studied, but it is plausible that an early start, at least before the onset of irreversible organ damage, will prove to be the best strategy. The case histories of two siblings with MPS I who started ERT at different ages support this hypothesis [14].

A delayed diagnosis that impedes early treatment is common in all MPS I phenotypes due to the rarity of the disease and the often non-specific presenting signs and symptoms [15]. A number of studies have focused on the optimal approach for sensitive and specific NBS for MPS I [16–19], and several NBS pilot programs that include MPS I screening have recently begun [1,20,21]. However, discussions on including MPS I in NBS programs will raise ethical issues, including the drawbacks of early detection in patients with late-onset, attenuated phenotypes [22–25], that need to be addressed.

In questionnaire studies, patients and their parents generally express strong support for expanding NBS programs for 'their' disorder (e.g., cystic fibrosis, Duchenne's muscular dystrophy, Pompe disease and the 22q11 deletion syndrome) [26–29]. An Australian postal survey of parents of MPS patients and adult MPS patients revealed an almost uniform support for introducing MPS I into NBS programs [30]. However, patients' attitudes toward genetic testing do not necessarily reflect their actual behavior [31,32]. Therefore, we conducted an interview-based qualitative study to explore the experiences of MPS I patients and parents. Qualitative research offers insight into emotional and experiential phenomena of interviewees, providing more in-depth understanding of a given research problem [33]. To enrich and nuance the ethical discussion about including MPS I in NBS programs, we focused primarily on diagnostic timing.

2. Methods

2.1. Patients

This study was conducted at the Academic Medical Center (AMC) in Amsterdam, one of the two national referral centers for MPS I patients in the Netherlands. The participants were recruited by one of the authors (MHdR), a pediatrician involved in the clinical care of children with MPS I and in MPS I-related research. The eligible participants received a phone call from MHdR announcing the study, and an informational letter explaining the study's goals and the voluntary nature of the interviews was subsequently sent. In this study, we approached the parents of patients across the entire disease severity spectrum and both adolescent and adult MPS I-S patients. In addition, one teenage patient, who had an HSCT at the age of three to treat an MPS I-H/S phenotype and who later received ERT due to graft failure, was invited to participate in the study. The study was approved by the Medical Ethics Committee of the AMC.

2.2. Data collection

Semi-structured interviews were conducted between July 2011 and October 2011 by a single researcher (MHdR), who has been trained in qualitative research methods. The interviews took place either at the patients' homes or at the hospital, depending on the parents' or patients' preferences. The voluntary nature of participation was emphasized at the beginning of the interview, and the patients were informed that the interview would be confidential and analyzed anonymously. A topic list was composed by MHdR, MGB (a medical doctor and qualitative researcher), FAW (a pediatrician and MPS I expert) and MCBvZ

(a medical ethicist and qualitative researcher) (Table 1). This topic list was used to guide the interviews. All of the questions were open-ended, and the parents and patients were encouraged to share their personal experiences with the interviewer. The interviewer kept field notes describing the interview setting to facilitate reproducing the interview context, if relevant. All of the interviews were audio-recorded. We enrolled patients in the study until the interviews provided no new information relevant to the research question.

2.3. Data analysis

SPSS version 19.0 was used to calculate the descriptive statistics for the patient characteristics. The data are presented as medians with ranges. All of the audio-recorded interviews were transcribed verbatim. The transcripts were transferred to MAXQDA 10 (www.maxqda.com), a software program that facilitates qualitative research analysis. Three interviews were openly and independently coded by two researchers (MGB and MHdR). To prevent unintentional response bias from question phrasing, the interview styles of three interviews were assessed by an additional researcher (MCBvZ). MHdR performed axial coding to develop a code tree [34]. This process led to identifying the major themes most relevant to the research question in this study, and five relevant themes were eventually identified. The Results section is structured according to these five themes.

3. Results

The patient characteristics are summarized in Tables 2 and 3. Eighteen MPS I patients and/or their parents were approached (6 MPS I-H, 4 MPS I-H/S and 8 MPS I-S patients). Of these 18 patients, two were MPS I-H/S twins, and four were MPS I-S sibling pairs. One adult MPS I-S patient did not respond to our invitation to participate. Of the 17 remaining patients, six teenage and adult patients (1 MPS I-H/S and 5 MPS I-S patients) and 13 parents of patients across the entire phenotypic spectrum were interviewed. The median age at the time of the study of the 17 patients who participated was 9 years (range, 3 to 44 years).

Fourteen patients (6 MPS I-H, 3 MPS I-H/S and 5 MPS I-S patients) were diagnosed with MPS I as a result of diagnostic work-ups motivated by clinical signs and symptoms. Two patients (MPS I-S) had been diagnosed through family screening after the MPS I diagnosis of a sibling. One MPS I-H/S patient, who had an HSCT at the age of 3, had been diagnosed as a result of metabolic screening because of only failure to thrive. The median age at diagnosis of the patients who were diagnosed from diagnostic work-ups motivated by clinical signs and symptoms was 0.9 years for the patients with MPS I-H, 3.8 years for the patients with MPS I-H/S and 9.0 years for the patients with MPS I-S.

From the qualitative analysis of the interviews, we identified five themes relevant to the aim of this study. These themes focused on the disadvantages experienced due to delayed diagnosis and the advantages and possible disadvantages of a hypothetical earlier diagnosis.

Table 1

The interview topic list.

A. Introduction by the researcher
- Emphasis on voluntary participation
- Emphasis on confidentiality
- Short explanation of the study's goals
B. Open-ended questions
- How was the course of disease before the diagnosis?
- How was the timing of the diagnosis experienced?
- How did you experience the period before the diagnosis?
- How do you experience the burden of the disease?
- How do/did you experience the burden of the disease treatment?
- What would it have meant to you if the diagnosis had occurred earlier?

Table 2
The characteristics of the MPS I patients.

	n (%)
Gender, male	6 (35%)
Gender, female	11 (65%)
Age in years (range)	9 (3–44)
MPS I-H	6 (35%)
MPS I-H/S	4 (24%)
MPS I-S	7 (41%)
Treatment with ERT	11 (65%)
Treatment with HSCT	6 (35%)
Age at diagnosis in years (range)	
- MPS I-H	0.9 (0.7–2.1)
- MPS I-H/S	3.7 (0.4–3.8)
- MPS I-S	5.0 (2.2–12.5)
Age of symptom onset in years ^a (range)	
- MPS I-H	0.1 (0.1–0.3)
- MPS I-H/S	0.7 (0.2–1.0)
- MPS I-S	0.7 (0.1–3.0)
Time from symptom onset to diagnosis in years (range)	
- MPS I-H	0.7 (0.6–1.8)
- MPS I-H/S	2.8 (0.2–2.8)
- MPS I-S	4.6 (0.7–12.2)
Diagnosis through family screening	2 (12%)
Diagnosis in response to symptoms	15 (88%)

The data are medians and ranges.

^a Retrospective age at symptom onset.

3.1. Delayed diagnosis causing parental frustration

A vivid picture of the impact of uncertainty during the period after symptom onset but before diagnosis emerged from the interviews. The parents often experienced a long ‘diagnostic odyssey’—a protracted search for an explanation of a health problem—because their child’s

Table 3
An overview of the patients.

Patient	MPS I phenotype	Age at diagnosis (years)	Age at symptom onset ^a (years)	Diagnosis	Presenting symptoms
1	S	12.5	0.3	Symptoms	Hip dysplasia
2	H	2.1	0.3	Symptoms	URTI/FD/inguinal hernia
3	H	1.0	0.3	Symptoms	URTI/FD
4	S	9.0	0.7	Symptoms	Motor delay
5	H/S	3.8	1.0	Symptoms	Joint stiffness
6	H/S	3.8	1.0	Symptoms	Joint stiffness
7	H/S	0.4	0.2	Symptoms	FTT
8	H	0.8	0.1	Symptoms	Failed hearing screening
9	H	0.7	0.1	Symptoms	URTI/FD
10	H	0.7	0.1	Symptoms	URTI/‘crying baby’
11	S	4.7	1.0	Symptoms	Inguinal hernia
12	S	2.2	0.7	Family screening	URTI/umbilical hernia
13	S	10.8	3.0	Symptoms	Joint stiffness
14	H/S	3.5	0.3	Symptoms	Developmental delay
15	H	1.3	0.1	Symptoms	Failed hearing screening
16	S	5.0	0.4	Symptoms	Umbilical/inguinal hernia
17	S	3.0	0.1	Family screening	FD

H = MPS I-Hurler.

H/S = MPS I-Hurler/Scheie.

S = MPS I-Scheie.

URTI = upper respiratory tract infections.

FD = feeding difficulties.

FTT = failure to thrive.

^a Retrospective age at symptom onset.

signs and symptoms were not recognized by physicians as being caused by MPS I. In general, patients across the entire phenotypic spectrum were frequently seen by a number of different specialists and were often hospitalized a number of times before the MPS I diagnosis was finally made. Although the concerns of several of the parents were recognized, many other potential diagnoses, such as cystic fibrosis, Down syndrome, juvenile rheumatoid arthritis, asthma and growth hormone deficiency, were considered before the correct diagnosis was made.

“Well, the pediatrician knew that there was something wrong, but she just couldn’t put her finger on what was actually wrong.” (the parent of an MPS I-H patient)

“And they kept saying: ‘it’s the asthma, the asthma, that’s why she’s not on track with her motor development’.” (the parent of an MPS I-S patient)

“We were referred to the pediatrician, and we remained under his care for more than one year because he thought there was a growth hormone problem or that kind of thing.” (the parent of an MPS I-S patient)

In addition, the medical specialists frequently suspected that there was no underlying disease, and some parents were told that their child would outgrow symptoms such as motor delay and repeated upper respiratory tract infections. During this period, almost all of the parents felt that there was something wrong with their child, which led to feelings of powerlessness and frustration.

“We went to the clinic, and we explained to them that she didn’t lift her head and that when you put her down like this, she didn’t move spontaneously. ‘Oh, it will happen’, they said. And this went on for two years: ‘it will happen’. And whatever you did, stay polite, become angry, or even become spitting mad, nothing helped.” (the parent of an MPS I-H/S patient)

“A young baby with a runny nose, coughing and sneezing...and when I informed the doctors of this, they just said: ‘well, it’s the time of the year, it happens in young children’. Even if I told them that this had been going on for three months, they said it was normal. And in my opinion, it wasn’t normal.” (the parent of an MPS I-H patient)

Moreover, the parents frequently felt that they were not being taken seriously at all by various specialists, which aggravated their feelings of impotence and distress.

“We had to fight for eight months to prove there was something wrong. And sometimes we were just told ‘you’re overreacting, there’s nothing there, she’s had a difficult start and she has to do it’. And for such a long time you lived in uncertainty, even though you knew there was something wrong. But you can’t pinpoint the problem or the extent of it, let alone where it originated. And yes, it pretty much comes down to feeling powerless and frustrated - that’s what you end up with.” (the parent of an MPS I-H patient)

“Very powerless...after all those years of experience, I just know that you should never dismiss your maternal instinct, that it does actually come from somewhere for a reason. But yeah, I absolutely did not feel that I was being heard.” (the parent of an MPS I-S patient)

In some cases, the mothers were labeled ‘overanxious’ by the specialists. One mother stated the following:

“I’ve seen all sorts of doctors for my child, and at a certain point, they pretty much said ‘madam, please stop dragging your child to the hospital’.” (the parent of an MPS I-S patient)

The feeling that they could not get the best care for their child until a correct diagnosis was made also led to feelings of impotence and frustration in some parents.

“Yes, feeling powerless, as a parent. You can't give your child the best you want to, I think. It makes you feel powerless and frustrated.” (the parent of an MPS I-H patient)

One mother described the period before the final diagnosis as causing more distress than the final diagnosis itself:

“It's been a prolonged process, and I can tell you that despite the fact that the diagnosis was a heavy burden because it's something where you're powerless to give direct help, the period before the diagnosis was even more difficult because you didn't know what you were fighting with, what the underlying problem was.” (the parent of an MPS I-H patient)

However, some participants described the advantages of having experienced a ‘diagnostic odyssey’. They felt that these experiences had helped them to manage the burden of the final diagnosis and the impact of the disease and its treatment, and they expressed concerns that an early diagnosis, especially one occurring shortly after birth, might have been more challenging for them.

“We have now had a lot of time to read up on his illness and slowly let it sink in. And if you let newborn screening bring this to light at an earlier stage, then that can be quite a blow without even realizing what you're actually dealing with yet.” (the parent of an MPS I-H patient)

“When we received the diagnosis, we felt recognized in our concerns and also felt kind of relieved. But you might not feel the same if a diagnosis is made very early in life because you don't know your child yet, so it's hard to believe that your child is sick.” (the parent of an MPS I-H patient)

3.2. Delayed diagnosis causing patient frustration

The interviews with two of the six attenuated patients revealed valuable information about the diagnostic process. From these interviews, it became clear that the negative impact of growing up with unrecognized (attenuated) MPS I was rather similar to the negative parental experiences with delayed diagnoses. These patients described a sense of frustration and powerlessness, and they frequently felt misunderstood before the diagnosis was made.

“For years I wondered: ‘what's wrong with me, why am I short, why can't I play sports or anything like that?’ and ‘why does everyone look at me funny’, you know? Like, you can't do this or you can't do that. And that's not pleasant....I didn't feel I was overreacting, I just always thought, well I just can't do it, you know. So then I again felt a little powerless.” (an MPS I-S patient)

“Well, I think because it was all so vague that you were not able to explain it to other people. That's why they misunderstood me, and as a result they often said ‘come on, you can do that’. Or they were a little overprotective and told me not to do things, while I could....I felt like a constant failure, never really being able to fulfill expectations.” (an MPS I-S patient)

One patient mentioned that the correct diagnosis was helpful for understanding several complaints and for proving that she had not been ‘overdramatic’.

“I was 12 at that time, so rather old, while I'd been suffering from different complaints for a long time. And I was told that it was all in my

head and so on. So then, I finally knew that all of this was because of the disease, and that it wasn't in my head. For me, that was rather comforting.” (an MPS I-S patient)

The other patient felt that she would have been better able to recognize and understand her limitations if she had had an earlier diagnosis.

“I think it would have made a difference. In any case, I could have been clearer towards those around me on what I could and couldn't do. For me, it was also a case of continuously pushing by boundaries. And I crossed a lot of them too, enough to make me feel that it's a shame, that it cost me a lot of energy, while maybe back then I could have said ‘No, I can't do that.’ I've never actually been able to say that.” (an MPS I-S patient)

3.3. Early diagnosis enabling reproductive decision-making

Another important theme identified by the parents was the impact of the (lack of) potential for family planning. The majority of the parents mentioned that early diagnosis would have facilitated reproductive choices.

One participant mentioned that she would have been able to choose between having more children (and assuming the risk of having another affected child) or deciding not to have more children.

“If I'd have known sooner that the following pregnancies would also involve a high-risk for the same diagnosis, I would have been able to make the choice to stop at one child and not have children anymore. I could not make that choice because the diagnosis was long overdue. If she had been diagnosed shortly after her birth, then we would also have had a choice to decide if we wanted to take on another sick child.” (the parent of an MPS I-H patient)

One parent of two children with MPS I-S expressed how she might not have had her second child if she had known about the risk of having a child with MPS I earlier.

“But I honestly have to say that I have always said if I had known earlier, then there never would have been a second child. So then our second child would never have been here. So yeah...that's very strange.” (the parent of two MPS I-S patients)

A mother of two other MPS I-S patients mentioned that an earlier diagnosis of the first child would have facilitated prenatal testing.

“If it's possible at a very early stage, the parents still have a choice. And a parent may say ‘it doesn't matter to me, I want to have this child.’ And then the other parent can be given a choice and might say ‘I can't deal with that.’ It's very personal. I had no choice.” (the parent of two MPS I-S patients)

3.4. Early diagnosis allowing focusing on the diagnosis

When the parents were asked about their views on diagnostic timing and what a hypothetical earlier diagnosis would have meant for them, several reported that an earlier diagnosis would have allowed them to focus on their child and to give their child the best possible care rather than focusing on searching for a diagnosis.

“You would be able to focus much more on the child than on the symptoms, trying to figure out ‘who do I approach now just to get a step further.’” (the parent of an MPS I-H/S patient)

The parents mentioned that an earlier diagnosis would have helped them to understand and recognize the limitations of their

child. One parent mentioned the guilt that she felt after her daughter had been diagnosed:

“Being able to fully accept her, with her limitations. And I feel sorry for her, that she...yes, like we let her down. And that wouldn't have been necessary.” (the parent of an MPS I-S patient)

Some parents felt that an earlier diagnosis would have allowed better life planning for issues such as schooling. One parent stated the following:

“Well, we have always let her join in, in kindergarten, primary school and sometimes we've thought ‘is it not too heavy or...’. And if you would have known beforehand that she was ill, then you might have opted for special education. And that remains the question - now she lags behind because she was always a little different or it was more difficult to join in - then she may have been the best among a group of children who all have disabilities.” (the parent of an MPS I-S patient)

A delayed diagnosis was thought to have a substantial negative impact on the well-being of the family, as reported by the majority of the participants. A mother expressed her feelings about the strain that the ‘diagnostic odyssey’ had placed on her family, and mentioned the potential positive impact of a hypothetical earlier diagnosis on her family situation:

“That could have saved me the worries, the physical problems, the psychological problems, because it all drags you down. And every time you find yourself drifting away, and you pull yourself up again by saying ‘Okay, we have to keep moving on.’ It was the powerlessness, everything really, the care, the future, what is your child's life expectancy? And if all the unanswered questions could have been answered sooner, my family situation would be completely different.” (the parent of an MPS I-H patient)

A minority of the respondents stated that if a diagnosis had been made earlier, it might have taken away a carefree period in their lives. In these cases, an early diagnosis might have increased parental anxiety.

“That you were able to enjoy your young child, as long as they are small. Without too many worries. There are pros and cons, definitely... It would have given me a certain peace, but of course there would have been other concerns instead, so yes, it depends on how you look at it.” (the parent of an MPS I-S patient)

“So, until three years of age, they were able to enjoy my early childhood, and the carefree thoughts of having a healthy child.” (an MPS I-S patient, talking about her parents)

In this respect, the need for proper information and support along with the MPS I diagnosis was mentioned by some of the parents based on their own, sometimes negative, experiences.

“I believe that being given bad news is always very serious for the parents, but you can't ignore it. This can, at least partially, be overcome by giving proper support, and provide the parents with a lot of information. That's what helped us a lot.” (the parent of an MPS I-H patient)

“The worst problem after diagnosis was the lack of information. That was probably the worst thing we had to deal with at that time.” (the parent of an MPS I-S patient)

These parents emphasized that the need for proper information and support might become even greater when a MPS I diagnosis is made early in life, such as shortly after birth.

3.5. Early diagnosis enabling timely start of treatment

Most of the respondents considered initiating treatment early to be an important advantage of early diagnosis. The parents felt that early medical treatment would have prevented disease progression and thus significant harm.

“Because if it's the case that the earlier the enzyme therapy is started, the more can be saved, yes well, the sooner it should of course be started.” (the parent of an MPS I-S patient)

“Also because time was a factor. The doctors were very clear about that, she needs to be transplanted before the age of two. But I noticed that she was exhibiting various changes after seven, eight months already, in the way she walked, in her fingers, in her joints. Her belly, her head, altogether should not have been necessary in my opinion. The sooner the better. And much later, after the transplants, thankfully I saw progress in the diagnostic period, that other children were being treated much sooner, well before they were affected by the disease. And they, of course, have less severe disabilities. That is why I feel like it would have been important to know sooner.” (the parent of an MPS I-H patient)

In addition, some parents mentioned that starting treatment earlier would have made it easier for their child to cope with the burden of treatment and consequently would have made it easier for them.

“Maybe if he would have been a little bit younger and a lot of it would have passed him by. Now he remembers everything; that he had a nasogastric tube and that he was very ill. And maybe if you experience this as a baby, a lot of it just passes you by.” (the parent of an MPS I-H patient)

“I think the younger they are the less they are aware of. For the parent, it's more bearable too. If your child does not object it's also more acceptable to say ‘okay, I'd like to commence this treatment with my child.’” (the parent of an MPS I-H patient)

However, the potential benefits of early treatment initiation were also contrasted with the potential burdens of treatment. Two of the parents stated the following:

“I think the disadvantage would be that they had to start with intravenous therapy sooner, that they had all these commitments up front because it's quite heavy going every week. I think that would be a disadvantage.” (the parent of two MPS I-S patients)

“The problem is, the first years are the best years, and the current treatments are not great... You just know you're taking away the best years... because that bone marrow... is not the full solution yet. The sooner you give that bone marrow... the better it is, but... you go straight to the hospital of course. The bone marrow transplantation is not without consequences, or without risks.” (the parent of an MPS I-H patient)

4. Discussion

This study was conducted to explore the experiences of MPS I patients and their parents with the timing of their diagnoses, and the goal was to enrich and nuance the ethical debate about expanding NBS programs for MPS I. In a questionnaire study, Hayes et al. demonstrated that parents of MPS patients are highly supportive of including MPS in NBS programs [30]. However, our interview study is the first in which the perceptions of MPS I patients and their parents about the timings of their diagnoses were investigated. We chose to use a qualitative research method because of its ability to describe the participants' experiences, which results in a more in-depth understanding of the

impact of the relevant themes. We conducted 17 interviews and identified five themes that are highly relevant to this discussion. Overall, the respondents' experiences with diagnostic timing were similar, both for the individual phenotypes and for the group as a whole.

This study confirms a recent report from the MPS I Registry that diagnostic delay is the rule rather than the exception for MPS I [15]. In the subgroup of our patients who were diagnosed from work-ups motivated by clinical signs and symptoms, the time to diagnosis was, as expected, shortest for the most severe (MPS I-H) phenotype and longest for the most attenuated (MPS I-S) phenotype. The time to diagnosis ranged from 7 months in two MPS I-H patients to 12 years in one MPS I-S patient. Unfortunately, the data from the Registry show that the median age at diagnosis has not decreased over the years for any of the MPS I phenotypes, despite the available treatment options [15].

A significant patient and parental impact from this diagnostic delay in MPS I has been reported by Hayes et al. [30] and was felt by many of the parents and patients in our study. The parents reported that they had suffered considerable distress due to the delay in diagnosing their sick child. The majority of the parents mentioned feeling that they were not being taken seriously by medical specialists during this 'diagnostic odyssey', which involved many misdiagnoses and led to strong feelings of powerlessness and frustration. Some parents also commented on the impact of the delayed diagnosis on daily family life and their own well-being. In addition, some parents experienced guilt because they felt unable to provide their child with the best possible care and support due to the cause their child's symptoms remaining unknown for a relatively long period. As a consequence, the correct diagnosis brought feelings of relief to some parents. The MPS I-S patients often felt misunderstood during the periods before their diagnoses, and the correct diagnosis helped to relieve these feelings. A major benefit of NBS will thus be eliminating the considerable distress associated with a delayed MPS I diagnosis. It is important to emphasize that negative experiences with diagnostic delay occurred in all of the phenotypic subgroups. Although the parents of the MPS I-H patients were confronted with a more severe and earlier onset of symptoms, it was evident that the parents of mild to moderately affected patients also experienced significant distress due to the long and uncertain diagnostic process.

Our results confirm those of D'Aco et al., who showed that late diagnosis is caused by a lack of MPS I disease awareness among medical specialists [15]. It is disappointing to note that this lack of awareness appears to have remained unchanged over recent decades even though the availability of disease-modifying treatments has led to a number of MPS I awareness campaigns in the Netherlands and elsewhere. These awareness campaigns were intended to increase recognition of the clinical red flags by non-MPS I specialists, such as general pediatricians and rheumatologists, and they seem to have been largely ineffective. A similarly disappointing unchanged diagnostic delay despite increasing awareness has been recently reported for late-onset Pompe disease, another LSD [35].

The availability of disease-modifying treatments for all of the phenotypic subtypes was identified by the parents and patients in our study as an important argument in favor of early diagnosis. Indeed, the direct medical benefits to the screened children have traditionally been the most important justification for including a disease in an NBS program. However, this argument in favor of early diagnosis should be placed in the context of the availability of universal health care coverage in the Netherlands, resulting in full access to all treatment options. Some parents mentioned the potential loss of a care-free period and an early confrontation with the disease burden as possible drawbacks of an earlier diagnosis. However, they believed that these drawbacks do not outweigh the benefits of early diagnosis followed by early treatment and that it could probably largely be overcome by offering optimal support and information along with the MPS I diagnosis.

First-tier screening for MPS I by NBS will not distinguish between the MPS I-H patients, who will benefit from early HSCT, and the more attenuated MPS I-H/S and MPS I-S patients, who may benefit from early ERT [7]. Although second-tier screening by genotyping will allow the phenotype to be predicted in a number of patients [36,37], phenotypic classification at diagnosis will not be feasible in a significant number of cases. Adding MPS I to NBS programs may therefore result in parental anxiety over the uncertain phenotype and optimal treatment strategy. Moreover, it is plausible that very mild forms of the disorder, which may remain asymptomatic for many years or even throughout life, will be detected [24,25,38]. In addition, the burden associated with false-positive NBS results, which may result in significant parental psychological stress [39], needs to be considered. Therefore, if MPS I would be included in NBS programs it will be paramount to have both well-controlled follow-up protocols in place for all individuals diagnosed with biochemical IDUA deficiencies, and support programs for families of newborns with a false positive-screening result. Guidelines for managing presymptomatic patients with various LSDs, including MPS I, have recently been published [40].

We deliberately chose an open-ended approach in our interview study to prevent unintentional response bias. Because the focus of our qualitative study was on eliciting the respondents' experiences with diagnostic timing, we encouraged the interviewees to describe these experiences rather than asking their opinions on including MPS I in NBS programs. From the respondents' overall responses, it became clear that a large majority of our participants were highly supportive of earlier diagnosis in MPS I. We ensured that the patients we recruited represented the entire spectrum of the disease, and, given the rarity of the disease, we were able to include a relatively large group of patients. Therefore, our results can probably be generalized to the entire population of MPS I patients and their parents.

5. Conclusion

This is the first study to examine the experiences of MPS I patients and their parents with diagnostic timing. Five important themes were identified. These themes reflect the perceived disadvantages of delayed diagnosis and the possible advantages of early diagnoses in our group of study participants. In addition, the possible disadvantages of early diagnoses were described. These themes are considered highly relevant to the ethical discussion about including MPS I in NBS programs. Overall, our results strongly support the importance of an early diagnosis in MPS I, an argument which is in favor of including MPS I in NBS programs.

Competing interests

FAW has received reimbursement of expenses and honoraria for lectures on the management of lysosomal storage diseases, including MPS I, from Genzyme Corp., USA. MHdR received a travel grant from Genzyme Corp., USA. MGB and MCBvZ declare to have no conflicts of interest.

Author's contributions

MHdR participated in the study design, recruited patients for the study, conducted the interviews, performed the analyses and drafted the manuscript. MGB participated in the study design and analyses and helped to draft the manuscript. FAW and MCBvZ conceived the study, participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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