



Psychosocial Functioning in Parents of MPS III Patients

Thirsa Conijn • Stephanie C. M. Nijmeijer •
Hedy A. van Oers • Frits A. Wijburg • Lotte Haverman

Received: 16 April 2018 / Revised: 30 May 2018 / Accepted: 04 June 2018 / Published online: 07 July 2018
© Society for the Study of Inborn Errors of Metabolism (SSIEM) 2018

Abstract Background: Mucopolysaccharidosis type III (MPS III or Sanfilippo syndrome) is a lysosomal storage disease resulting in progressive neurocognitive decline during childhood and early demise. Its diagnosis may have a great impact on parents, potentially leading to psychosocial problems such as anxiety, depression, parental distress, and posttraumatic stress.

Methods: Twenty-six mothers and 19 fathers of 34 Dutch MPS III patients completed the “Hospital Anxiety and Depression Scale” (HADS), the “Distress Thermometer for Parents” (DT-P), and the “Self-Rating Scale for Posttraumatic Stress Disorders” (SRS-PTSD). Independent-sample T-tests and chi-square tests were used to assess differences between parents of MPS III patients and reference groups regarding anxiety and depression (HADS), distress (DT-P), and posttraumatic stress (SRS-PTSD).

Results: Mothers met the criteria for clinically relevant anxiety (50%) and depression (34.6%) more frequently compared to reference mothers ($p = 0.001$). Fathers more often met the criteria for clinically relevant depression (36.8%) compared to reference fathers ($p = 0.022$). Clinically relevant distress was highly prevalent in mothers (84.6%) and fathers (68.4%) of MPS III patients compared

to reference parents ($p < 0.01$). Finally, the prevalence of PTSD was strikingly higher in both mothers (26.9%) and fathers (15%) than reported in the general Dutch population (respectively, $p < 0.001$ and $p < 0.05$).

Conclusions: We report a clinically relevant impact of parenting an MPS III patient on psychosocial functioning, which is demonstrated by high levels of anxiety, depression, distress, and a remarkably high prevalence of PTSD. Structural monitoring of the psychosocial functioning of MPS III parents is therefore essential and may be beneficial for the whole family.

Introduction

Mucopolysaccharidosis type III (MPS III or Sanfilippo syndrome) is a lysosomal storage disease primarily characterized by progressive neurocognitive decline during childhood (Shapiro et al. 2016). The first phase of the disease manifests after a seemingly normal development during the first 2 years of life, followed by a slowing of cognitive development. The second phase is characterized by severe sleeping problems, behavioral problems, and progressive cognitive decline. In the final phase of the disease, motor skills are lost and patients become fully care dependent and bedridden (Cleary and Wraith 1993). No disease-modifying treatment is yet available and patients usually die in the second or third decade of life (Shapiro et al. 2016). The diagnosis of this devastating disease may have great impact on the parents and the family. Raising a chronically ill child requires parents to act in multiple roles involving complex responsibilities, such as management of the disease and caring for healthy siblings (Hatzmann et al. 2008). Parents of chronically ill children are at a greater risk

Thirsa Conijn and Stephanie C. M. Nijmeijer contributed equally to this article.

Communicated by: Roberto Giugliani, MD, PhD

T. Conijn • S. C. M. Nijmeijer • F. A. Wijburg (✉)
Department of Pediatric Metabolic Diseases, Emma Children’s Hospital and Lysosome Center ‘Sphinx’, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
e-mail: f.a.wijburg@amc.uva.nl

H. A. van Oers • L. Haverman
Psychosocial Department, Emma Children’s Hospital, Academic Medical Center, Amsterdam, The Netherlands

for psychosocial problems such as depression, anxiety, cognitive problems, and parental distress (Cousino and Hazen 2013; Murphy et al. 2007; van Oers et al. 2014). Finally, parents frequently face potentially traumatic events (e.g., receiving the initial diagnosis), followed by short- or long-term stress responses (Kazak et al. 2006). Studies evaluating the psychosocial functioning of parents of MPS III patients reported elevated levels of parental distress, depression, and anxiety (Grant et al. 2013; Kalkan Ucar et al. 2010; Malcolm et al. 2012; Somanadhan and Larkin 2016). However, these studies comprised small sample sizes and results were not compared with data on parents of healthy children. In addition, previous studies made no distinction between mothers and fathers, which may be of interest as studies focusing on other disorders identified significant gender differences in psychosocial experiences of parents (Clarke et al. 2009; Marchal et al. 2017). As detailed knowledge about the psychosocial functioning of parents of MPS III patients will help to organize appropriate (psychosocial) support and interventions, we aimed to assess anxiety, depression, and parental distress, as well as posttraumatic stress symptoms, in mothers and fathers of MPS III patients compared to Dutch reference groups.

Methods

Participants and Procedures

Parents of all living MPS III patients under care at the Academic Medical Center (AMC), Amsterdam, were invited by letter to participate in this cross-sectional study. Parents who gave permission to participate received an e-mail with a personal link to online questionnaires. Before starting the questionnaires, online informed consent was obtained. The data collection was performed in accordance with the regulations of the Medical Ethics Committee of the AMC, the Netherlands.

Measures

Sociodemographic Characteristics

Since this study involves a relatively small sample size and the members of our research group know all parents, we did not collect sociodemographic data of nonparticipating parents to guarantee the anonymous nature of the study. Age, gender, educational level, and marital status from participating parents were collected with a sociodemographic questionnaire.

Anxiety and Depression

Anxiety and depression were measured with the “Hospital Anxiety and Depression Scale” (HADS) (Bjelland et al. 2002). This questionnaire consists of 14 items with a four-point Likert scale (0–3) divided into two subscales measuring symptoms of anxiety and depression experienced during the previous week, resulting in scores from 0 to 21 for each subscale. Mean scores on the subscales were calculated, and the proportion of parents with clinically relevant anxiety and/or depression (score of >8) was reported. The Dutch version of the HADS has shown to be valid and reliable (Spinhoven et al. 1997). The Cronbach’s alpha values in the present study were good (0.81–0.91). Results were compared to Dutch reference parents (Vingerhoets 2012).

Parental Distress

Parental distress was measured with the “Distress Thermometer for Parents” (DT-P) (Haverman et al. 2013). The DT-P consists of a thermometer score where parents were asked to rate their overall distress (0 = *no distress* to 10 = *extreme distress*). Distress was indicated as clinically relevant from a score ≥ 4 . The thermometer was accompanied by a problem list (parents indicated whether they had experienced any of the listed problems during the previous week) divided over six problem domains: practical, family/social, emotional, physical, cognitive, and parenting. The problem domain scores were the sum of the dichotomous items (0 = *no* and 1 = *yes*) in each problem domain. Three additional questions about perceived support and wish for referral were asked.

The DT-P is a well-validated short screening instrument to identify the level of distress in parents of children with a chronic health condition (Haverman et al. 2013). The Cronbach’s alpha values in the present study were moderate to good (0.65–0.88). Results of parental distress were compared to Dutch reference parents of healthy children (van Oers et al. 2017).

Posttraumatic Stress

Posttraumatic stress symptoms were measured with the “Self-Rating Scale for Posttraumatic Stress Disorders” (SRS-PTSD) questionnaire (Carlier et al. 1998). Parents were asked to think of an event related to their child’s illness that has had the most impact on them. The SRS-PTSD is a self-reported questionnaire for adults and contains 17 items corresponding to the diagnostic DSM-IV

symptoms of PTSD: reexperiencing, avoidance, and hyperarousal. Symptoms experienced during the last 4 weeks were registered on a three-point Likert scale (0–2). Higher scores represent more posttraumatic stress symptoms. Parents met the criteria for PTSD if at least one reexperiencing, three avoidance, and two hyperarousal symptoms were present during the previous 4 weeks. The SRS-PTSD has shown to have adequate psychometric properties (Carlier et al. 1998). In the present study, Cronbach's alpha values were good (0.76–0.91). The prevalence of PTSD among the general Dutch population, measured with the same questionnaire, is known from the literature (Bronner et al. 2009).

Statistical Analyses

Statistical Package for Social Sciences (SPSS) (version 23.0, SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. First, descriptive statistics were used to describe the sociodemographic characteristics of parents and the reference groups. Baseline differences between parents and the reference groups were analyzed with independent-sample T-tests for continuous data and chi-square tests/Fisher's exact tests for categorical data.

Second, independent-sample T-tests were performed for continuous data and chi-square tests/Fisher's exact tests for categorical data to assess differences between parents of MPS III patients and reference parents on the outcomes of the questionnaires. Effect sizes (d) were calculated by dividing the difference in mean scores between the groups by the pooled standard deviation of both groups, to report the strengths of the differences. P -values <0.05 were considered statistically significant in all statistical analyses.

Results

Sociodemographic Characteristics

Fifty-seven parents of 37 patients with MPS III were invited for this study. Four parents declined participation as they indicated they were afraid that participation would be too stressful. Eight parents did not complete the online questionnaires (response rate 78.9%). Sixteen parent couples participated in this study (Table 1). Mothers and fathers were significantly older than those in the reference groups ($p \leq 0.001$). However, as the age of MPS III parents was not correlated with the scores on the questionnaires, no correction for age was used.

Table 1 Sociodemographic characteristics of mothers and fathers of MPS III patients and reference groups

	Mothers			Fathers		
	MPS III, $N = 26$	Reference HADS, $N = 368$	Reference DT-P, $N = 671$	MPS III, $N = 19$	Reference HADS, $N = 368$	Reference DT-P, $N = 463$
<i>Parents</i>						
Age in years, M (SD)	48.7 (10.2)	40.0* (8.2)	38.7* (6.4)	50.1 (9.6)	43.1* (8.5)	41.7* (7.4)
Educational level ^a , N (%)						
Low	7 (26.9)	121 (32.9)	88 (13.1)	2 (10.5)	116 (31.5)	72 (15.6)
Intermediate	9 (34.6)	147 (39.9)	300 (44.7)	7 (36.8)	129 (35.1)	193 (41.7)
High	10 (38.5)	100 (27.2)	281 (41.9)	10 (52.6)	123 (33.4)	190 (41.0)
Marital status, N (%)						
Married/living together	23 (88.5)	337 (91.6)	604 (90.0)	18 (94.7)	353 (95.9)	449 (97.0)
Single/separated	3 (11.5)	29 (7.9)	66 (9.8)	1 (5.3)	10 (2.7)	14 (3.0)
Other	0	2 (0.50)	1 (0.20)	0	5 (1.4)	0
<i>Child (N = 34)</i>						
Age in years, M (SD)	19.76 (9.5)					
age range	5–38					
Gender, male, N (%)	18 (52.9)					
MPS phenotype, N (%)						
Rapidly progressing (RP)	9 (26.5)					
Slowly progressing (SP)	25 (73.5)					

* $p \leq 0.001$, according to independent-sample T-tests

^aHighest level completed. *Low* primary education, lower and middle general secondary education, *intermediate* middle vocational education, higher secondary education, preuniversity education, *high* higher vocational education, university (CBS 2012)

Anxiety and Depression

Mothers of MPS III patients reported significantly higher mean levels of anxiety ($p < 0.001$) and depression ($p < 0.001$) than mothers in the reference group. In addition, they reported more frequently clinically relevant anxiety ($p = 0.001$) and clinically relevant depression ($p = 0.001$) than the reference group. Fathers reported more frequently clinically relevant depression compared to fathers in the reference group ($p = 0.022$) (Tables 2 and 3).

Parental Distress

Mothers and fathers of MPS III patients reported higher mean DT-P thermometer scores and more frequently clinically relevant distress compared to reference parents ($p < 0.01$). Moreover, mothers and fathers reported higher scores on all domains compared to reference parents ($p < 0.001$ – $p < 0.05$), except for the social, physical, and cognitive domain for fathers. Analyses of the individual problem domain items revealed that mothers of MPS III patients reported significantly more often problems on 24 out of 34 items ($p < 0.001$ – $p < 0.05$) and fathers on 15 out of 34 items ($p < 0.001$ – $p < 0.05$). The results of the additional questions showed that both mothers and fathers reported more often than reference parents to have problems with receiving sufficient support from people around them ($p < 0.001$) and

indicated more often a (probable) wish to talk to a professional about their situation ($p < 0.001$ – $p < 0.01$). Fathers more often reported that people in their surrounding react with a lack of understanding to their situation compared to reference fathers ($p < 0.05$) (Table 4).

Posttraumatic Stress

Ten parents (22%, 7 mothers and 3 fathers) met the criteria for the diagnosis of PTSD (Table 5). When compared to the prevalence of PTSD among the general Dutch population (3.8%) (Bronner et al. 2009), the prevalence in this study is significantly higher among mothers of MPS III patients compared to Dutch women (26.9% vs. 5.3%, chi-square $p < 0.001$) and among fathers of MPS III patients compared to Dutch men (15.8% vs. 2.2%, Fisher's exact $p < 0.05$).

Discussion

Our study investigated the psychosocial functioning of mothers and fathers of Dutch MPS III patients by measuring levels of anxiety, depression, parental distress, and posttraumatic stress. Firstly, we demonstrate significantly higher mean levels of anxiety and depression among mothers compared to reference mothers. Although not significant, the mean level of anxiety and depression among fathers are also notably higher compared to the reference

Table 2 Anxiety and depression (mean scores) in mothers and fathers of MPS III patients in comparison to reference parents^a

	Mothers		Fathers					
	MPS III, $N = 26$ M (SD)	Reference HADS, $N = 368$ M (SD) p d	MPS III, $N = 19$ M (SD)	Reference HADS, $N = 368$ M (SD) p d				
Anxiety	8.0 (4.3)	4.8 (3.5) <0.001 0.90	5.7 (3.9)	4.1 (3.7)	0.067	0.43		
Depression	6.0 (3.6)	3.1 (3.3) <0.001 0.87	5.8 (4.9)	3.6 (3.6)	0.069	0.60		

Effect size: d

Significant differences at $p < 0.05$ are presented in bold, according to independent-sample T-tests

^aHigher scores represent higher levels of anxiety and depression.

Table 3 Clinical scores of anxiety and depression in mothers and fathers of MPS III patients compared to reference parents^a

	Mothers					Fathers							
	MPS III, $N = 26$ N %	Reference HADS, $N = 368$ N % p OR 95% CI				MPS III, $N = 19$ N %	Reference HADS, $N = 368$ N % p OR 95% CI						
Anxiety	13 50	76	20.7	0.001	2.42	1.57–3.74	6	31.6	64	17.4	0.128	1.82	0.90–3.65
Depression	9 34.6	44	12.0	0.001	2.90	1.59–5.26	7	36.8	56	15.2	0.022	2.42 ^a	1.28–4.57

Significant differences at $p < 0.05$ are presented in bold, according to chi square tests

^aCutoff point for clinically relevant anxiety and depression: score of ≥ 8

Table 4 Parenting distress in mothers and fathers of MPS III patients compared to reference parents

	Mothers				Fathers			
	MPS III, N = 26	Reference, N = 671	p	OR/ES 95% CI	MPS III, N = 19	Reference, N = 463	p	OR/ES 95% CI
<i>Thermometer score, M (SD)</i>	5.96 (2.74)	3.51 (2.70)	<0.001	0.91	5.00 (2.75)	2.83 (2.53)	<0.001	0.86
Clinical, %	84.6	42.3	<0.001	2.0	68.4	32.2	0.001	2.13
<i>Total problem score, M (SD)</i>	11.38 (7.43)	5.42 (5.07)	<0.001	1.15	7.32 (6.52)	3.73 (4.17)	0.029	0.85
<i>Practical problems, M (SD)</i>	2.31 (2.13)	1.06 (1.31)	0.007	0.93	2.00 (2.36)	0.80 (1.18)	0.041	0.98
Housing, %	15.4	5.5	0.060	2.79	15.8	3.7	0.039	4.3
Work/study, %	26.9	25.3	0.855	1.06	42.1	25.9	0.117	1.63
Finances/insurance, %	11.5	16.7	0.601	0.69	15.8	14.5	0.747	1.10
Housekeeping, %	46.2	21.6	0.003	2.14	26.3	12.1	0.078	2.18
Transport, %	19.2	4.6	0.008	4.16	15.8	3.9	0.044	4.06
Child care/child supervision, %	50.0	10.1	<0.001	4.93	31.6	5.4	0.001	5.85
Leisure activities/relaxing, %	61.5	22.4	<0.001	2.75	52.6	14.9	<0.001	3.53
<i>Social problems, M (SD)</i>	1.04 (1.48)	0.39 (0.74)	0.035	0.83	0.68 (1.16)	0.28 (0.63)	0.144	0.62
Dealing with (ex)partner, %	23.1	12.4	0.128	1.87	10.5	11.7	1.00	0.90
Dealing with family, %	26.9	10.9	0.022	2.48	21.1	6.7	0.041	3.14
Dealing with friends, %	23.1	3.7	0.001	6.19	15.8	1.5	0.005	10.44
Interacting with your child(ren), %	30.8	11.8	0.010	2.61	21.1	7.8	0.063	2.71
<i>Emotional problems, M (SD)</i>	4.19 (2.77)	1.77 (2.12)	<0.001	1.13	2.42 (1.98)	1.08 (1.64)	0.001	0.81
Controlling emotions, %	53.8	27.4	0.003	1.96	52.6	11.9	<0.001	4.43
Self-confidence, %	46.2	22.7	0.006	2.04	15.8	12.7	0.724	1.24
Fears, %	53.8	10.7	<0.001	5.02	47.4	6.5	<0.001	7.31
Depression, %	65.4	31.9	<0.001	2.05	36.8	22.2	0.162	1.66
Feeling tense or nervous, %	69.2	36.1	0.001	1.92	36.8	26.3	0.311	1.40
Loneliness, %	30.8	7.7	0.001	3.97	15.8	3.7	0.039	4.30
Feelings of guilt, %	26.9	17.4	0.200	1.54	0.0	7.3	0.385	–
Use of substances (e.g., alcohol, drugs, and/or medication), %	3.8	2.7	0.519	1.43	10.5	3.0	0.127	3.48
Intrusive/recurrent thoughts about a specific event, %	69.2	20.4	<0.001	3.39	26.3	13.8	0.170	1.90
<i>Physical problems, M (SD)</i>	2.81 (2.00)	1.80 (1.71)	0.003	0.59	1.68 (2.19)	1.33 (1.46)	0.491	0.24
Eating, %	23.1	12.4	0.128	1.87	5.3	4.8	0.612	1.11
Weight, %	19.2	26.2	0.425	0.733	10.5	16.6	0.752	0.63
Sleep, %	57.7	29.7	0.002	1.95	42.1	21.4	0.046	1.97

(continued)

Table 4 (continued)

	Mothers				Fathers					
	MPS III, N = 26	Reference, N = 671	p	OR/ES	95% CI	MPS III, N = 19	Reference, N = 463	p	OR/ES	95% CI
Fatigue, %	76.9	55.7	0.033	1.38	1.11–1.72	42.1	44.1	0.866	0.96	0.56–1.64
Out of shape/condition, %	53.8	20.9	< 0.001	2.58	1.76–3.79	26.3	19.0	0.386	1.39	0.64–3.01
Pain, %	26.9	24.3	0.759	1.11	0.58–2.12	21.1	18.1	0.762	1.16	0.48–2.83
Sexuality, %	23.1	10.6	0.057	2.18	1.05–4.55	21.1	8.9	0.091	2.38	0.95–5.96
<i>Cognitive problems, M (SD)</i>	1.04 (0.87)	0.40 (0.70)	0.001	0.91	0.53 (0.84)	0.53 (0.84)	0.25 (0.55)	0.170	0.50	
Concentration, %	57.7	17.9	< 0.001	3.23	2.24–4.66	26.3	11.2	0.061	2.34	1.06–5.19
Memory, %	46.2	22.4	0.005	2.07	1.33–3.20	26.3	13.6	0.167	1.93	0.88–4.25
<i>Parenting problems^a, M (SD)</i>	2.27 (1.80)	0.34 (0.78)	< 0.001	2.30	2.42 (1.54)	2.42 (1.54)	0.32 (0.82)	< 0.001	2.48	
Dealing with your child, %	38.5	9.1	< 0.001	3.53	2.06–6.06	36.8	7.8	0.002	3.79	1.95–7.37
Dealing with the feelings of your child, %	57.7	7.7	< 0.001	6.21	4.09–9.44	63.2	6.9	< 0.001	7.30	4.53–11.77
Talking about the disease/consequences with your child, %	30.8	2.5	< 0.001	10.14	4.82–21.30	31.6	2.2	< 0.001	11.68	4.75–28.77
Independence of your child, %	69.2	6.3	< 0.001	9.23	6.26–13.60	78.9	6.0	< 0.001	10.43	6.82–15.96
Following advice about treatment/giving medication, %	30.8	2.8	< 0.001	9.07	4.39–18.75	31.6	2.4	< 0.001	10.62	4.40–25.65
<i>Additional questions</i>										
Enough support from surroundings, %	65.4	92.1	< 0.001	0.71	0.54–0.94	63.2	93.3	< 0.001	0.67	0.48–0.96
People react with a lack of understanding, %	23.1	11.3	0.109	2.04	0.98–4.24	26.3	10.2	0.043	2.59	1.17–5.77
Would like to talk to a professional about situation, yes/maybe %	69.2	17.1	< 0.001	4.04	2.98–5.48	36.8	12.5	0.008	2.94	1.56–5.56

Total problem score and problem domain scores were analyzed with independent-sample T-tests. The presence of a clinical thermometer score (≥ 4) and of reported problems (individual items) was analyzed with chi-square tests. Significant differences at $p < 0.05$ are presented in bold

^a Control parents in the domain “parenting problems” consisted of 560 mothers and 370 fathers

Table 5 Posttraumatic stress (symptoms) in mothers and fathers of MPS III patients

	Mothers (<i>N</i> = 26)		Fathers (<i>N</i> = 19)	
	<i>N</i>	%	<i>N</i>	%
Intrusions (≥ 1 symptom)	23	88.5	17	89.5
Avoidance (≥ 3 symptoms)	7	26.9	5	26.3
Hyperarousal (≥ 2 symptoms)	12	46.2	7	36.8
PTSD ^a	7	26.9	3	15.8

^a Criteria PTSD are met if at least one intrusion, three avoidance, and two hyperarousal symptoms have been present in the previous 4 weeks

fathers. Half of the mothers meet the criteria for clinically relevant anxiety and approximately one third of both mothers and fathers meet the criteria for clinically relevant depression. Twice as many fathers meet the criteria for clinically relevant anxiety compared to reference fathers, although this is not significant. These high levels of anxiety and depression are in line with previous research among parents of MPS III patients (Grant et al. 2013; Kalkan Ucar et al. 2010).

Secondly, more clinically relevant parental distress and problems on all life domains are found among both mothers and fathers compared to mothers and fathers of healthy children. The reported levels of parental distress are strikingly higher in comparison to those found in other studies on parents with chronically ill children (Basart et al. 2017; Haverman et al. 2013; Limperg et al. 2016). For instance, clinically relevant distress is reported in 63% of mothers and 59% of fathers of patients with pediatric cancer (Schepers et al. 2018) compared to, respectively, 85% and 68% of the mothers and fathers in our study. This is probably due to the fact that, in contrast to most of the other investigated disorders, MPS III is an invariably progressive, neurodegenerative, and ultimately fatal disorder with no disease-modifying treatment available (Shapiro et al. 2016). Thus, after receiving the diagnosis, parents face a very grim and uncertain future, without any hope for improvement or cure. In addition, severe behavioral difficulties and sleeping problems, which are common in MPS III patients (Valstar et al. 2008), are also reported to be associated with increased parental distress (Malcolm et al. 2012; Neece 2014; Somanadhan and Larkin 2016). Another striking conclusion is that approximately one third of both mothers and fathers indicate that they do not receive enough support from their surroundings.

Thirdly, the majority of the parents in this study report posttraumatic stress symptoms related to their child's illness

and an astonishing high percentage meet the criteria for PTSD.

We believe that our study adds important and new information to the existing scarce literature. First, we used a relatively large sample size compared to earlier quantitative studies. In addition, almost as many fathers as mothers participated in this study, whereas earlier studies included mostly mothers. The distinction between mothers and fathers is important, as the differences in experiences in psychosocial functioning should be addressed in the care for parents of chronically ill children (Marchal et al. 2017). Finally, we are the first to report on posttraumatic stress symptoms as a potential major factor in the psychosocial impact of being a parent of an MPS III patient, which may warrant a specific therapeutic approach.

Some limitations of the present study need to be discussed. Firstly, four parents declined participation as they felt too burdened, which could have led to selection bias. However, these parents may be even more affected by psychosocial distress than the participants, leading to an underestimation of the problem. Secondly, due to the fact that all data were coded, we are unaware of the disease phases the patients are currently in. Therefore, we cannot correlate the patients' disease phase with the psychosocial functioning of the parents. However, we believe that not the disease phase in particular is correlated to PTSD but the fact that these parents are exposed to prolonged stress due to multiple potential traumatic events (e.g., diagnosis, disease progression, disappointment about treatment possibilities) over the trajectory of the illness (Malcolm et al. 2012) which may impede with the normal diminishing stress response over time. Since this study only included parents of patients who are alive, a greater proportion of the patients with a rapidly progressing phenotype will have passed away, leading to an overrepresentation of patients with a slowly progressive phenotype. Finally, we do not know which event parents had in mind while completing the SRS-PTSD questionnaire. We did not want to introduce bias by providing potential events, such as the moment of diagnosis, since this varies per person.

It is noteworthy that, in our clinical experience, most parents do not have professional psychosocial support, even though 69% of the mothers and 37% of the fathers indicate that they (probably) would like to talk to a professional about their situation. Most parents indicate that the well-being of their child is the most important, which was also demonstrated in a previous study which reported that parents of MPS III patients often force themselves to retain a positive outlook in order to keep the family together (Somanadhan and Larkin 2016). This indicates that most parents are strong and resilient and have efficient coping strategies.

Despite this admirable coping, our data stress the importance of structural monitoring of the psychosocial functioning of these parents in daily clinical practice, as this may help to improve the well-being of parents and also of healthy siblings. Since parents often experience anxiety and stress following their child's diagnosis (Somanadhan and Larkin 2016), we propose to incorporate a medical psychologist consultation as standard of care immediately after the diagnosis. In addition, by using a short screening instrument such as the DT-P (Haverman et al. 2013), parents could be structurally monitored and those parents who need support may thus be identified (van Oers et al. 2014), followed by psychosocial support (for instance, referral to a clinical psychologist or social worker). Although most psychologists are not familiar with MPS III, local services should be able to provide treatment for anxiety, depression, distress, and/or PTSD.

Acknowledgments We would like to thank the parents who participated in this study and the Zabawas Foundation, the Zeldzame Ziekten Foundation, and Foundation Kinderen en Kansen for their financial support. Also, we thank Ad Vingerhoets for providing the HADS reference group.

Synopsis

Mothers and fathers of MPS III patients have an impaired psychosocial functioning, demonstrated by increased levels of anxiety, depression, distress, and a remarkably high prevalence of PTSD.

Details of Author Contributions

Thirsa Conijn and Stephanie Nijmeijer were involved in conception and design of this study, in analyses and interpretation of the data, and drafting the article. Lotte Haverman, Hedy van Oers, and Frits Wijburg were involved in the conception and design of this study, in analyses and interpretation of the data, and critically revising the article. All authors are in agreement with submission of this draft to JIMD reports. Frits Wijburg is the guarantor for this article.

Corresponding Author

F. A. Wijburg

Competing Interest Statement

The authors have no competing interests to declare.

Funding

This study was funded by grants from the private foundations Zabawas, Zeldzame Ziekten Fonds, and

Kinderen en Kansen, the Netherlands. The authors confirm independence from the sponsors; the content of the article has not been influenced by the sponsors.

Ethics Approval

The study was conducted in compliance with ethical standards.

Patient Consent

Informed consent was obtained from the participating parents.

Institutional Committee for Care and Use of Laboratory Animals

This article does not contain any studies with animal subjects performed by any of the authors.

References

- Basart H, van Oers HA, Paes EC et al (2017) Health-related quality of life in children with Robin sequence. *Am J Med Genet A* 173(1):54–61
- Bjelland I, Dahl AA, Haug TT, Neckelmann D (2002) The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 52(2):69–77
- Bronner MB, Peek N, Vries M, Bronner AE, Last BF, Grootenhuis MA (2009) A community-based survey of posttraumatic stress disorder in the Netherlands. *J Trauma Stress* 22(1):74–78
- Carlier IV, Lamberts RD, Van Uchelen AJ, Gersons BP (1998) Clinical utility of a brief diagnostic test for posttraumatic stress disorder. *Psychosom Med* 60(1):42–47
- CBS (2012) Onderwijsniveau bevolking gestegen. <https://www.cbs.nl/nl-nl/nieuws/2013/40/onderwijsniveau-bevolking-gestegen>. Accessed Sept 2017
- Clarke NE, McCarthy MC, Downie P, Ashley DM, Anderson VA (2009) Gender differences in the psychosocial experience of parents of children with cancer: a review of the literature. *Psychooncology* 18(9):907–915
- Cleary MA, Wraith JE (1993) Management of mucopolysaccharidosis type III. *Arch Dis Child* 69(3):403–406
- Cousino MK, Hazen RA (2013) Parenting stress among caregivers of children with chronic illness: a systematic review. *J Pediatr Psychol* 38(8):809–828
- Grant S, Cross E, Wraith JE et al (2013) Parental social support, coping strategies, resilience factors, stress, anxiety and depression levels in parents of children with MPS III (Sanfilippo syndrome) or children with intellectual disabilities (ID). *J Inher Metab Dis* 36(2):281–291
- Hatzmann J, Heymans HS, Ferrer-i-Carbonell A, van Praag BM, Grootenhuis MA (2008) Hidden consequences of success in pediatrics: parental health-related quality of life – results from the care project. *Pediatrics* 122(5):e1030–e1038
- Haverman L, van Oers HA, Limperg PF et al (2013) Development and validation of the distress thermometer for parents of a chronically ill child. *J Pediatr* 163(4):1140–1146.e1142
- Kalkan Ucar S, Ozbaran B, Demiral N, Yuncu Z, Erenmis S, Coker M (2010) Clinical overview of children with mucopolysaccharidosis

- type III A and effect of Risperidone treatment on children and their mothers psychological status. *Brain and Development* 32(2):156–161
- Kazak AE, Kassam-Adams N, Schneider S, Zelikovsky N, Alderfer MA, Rourke M (2006) An integrative model of pediatric medical traumatic stress. *J Pediatr Psychol* 31(4):343–355
- Limperg PF, Haverman L, Peters M, Grootenhuis MA (2016) Psychosocial functioning of mothers of boys with haemophilia. *Haemophilia* 22(1):e57–e60
- Malcolm C, Hain R, Gibson F, Adams S, Anderson G, Forbat L (2012) Challenging symptoms in children with rare life-limiting conditions: findings from a prospective diary and interview study with families. *Acta Paediatr* 101(9):985–992
- Marchal JP, van Oers HA, Maurice-Stam H, Grootenhuis MA, van Trotsenburg ASP, Haverman L (2017) Distress and everyday problems in Dutch mothers and fathers of young adolescents with down syndrome. *Res Dev Disabil* 67:19–27
- Murphy NA, Christian B, Caplin DA, Young PC (2007) The health of caregivers for children with disabilities: caregiver perspectives. *Child Care Health Dev* 33(2):180–187
- Neece CL (2014) Mindfulness-based stress reduction for parents of young children with developmental delays: implications for parental mental health and child behavior problems. *J Appl Res Intellect Disabil* 27(2):174–186
- Schepers SA, Sint Nicolaas SM, Maurice-Stam H, Haverman L, Verhaak CM, Grootenhuis MA (2018) Parental distress 6 months after a pediatric cancer diagnosis in relation to family psychosocial risk at diagnosis. *Cancer* 124(2):381–390
- Shapiro EG, Nestrail I, Delaney KA et al (2016) A prospective natural history study of mucopolysaccharidosis type IIIA. *J Pediatr* 170:278–287
- Somanadhan S, Larkin PJ (2016) Parents' experiences of living with, and caring for children, adolescents and young adults with mucopolysaccharidosis (MPS). *Orphanet J Rare Dis* 11(1):138
- Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM (1997) A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med* 27(2):363–370
- Valstar MJ, Ruijter GJ, van Diggelen OP, Poorthuis BJ, Wijburg FA (2008) Sanfilippo syndrome: a mini-review. *J Inher Metab Dis* 31(2):240–252
- van Oers HA, Haverman L, Limperg PF, van Dijk-Lokkart EM, Maurice-Stam H, Grootenhuis MA (2014) Anxiety and depression in mothers and fathers of a chronically ill child. *Matern Child Health J* 18(8):1993–2002
- van Oers HA, Schepers SA, Grootenhuis MA, Haverman L (2017) Dutch normative data and psychometric properties for the Distress Thermometer for Parents. *Qual Life Res* 26(1):177–182
- Vingerhoets AJJM (2012) Normdata HADS