

Assessing the burden on caregivers of MECP2 duplication syndrome

Muharrem Ak, Zekeriya Aktürk, Kristina Bowyer, Laurence Mignon, Sasidhar Pasupuleti, Daniel G. Glaze, Bernhard Suter, Davut Pehlivan

Angaben zur Veröffentlichung / Publication details:

Ak, Muharrem, Zekeriya Aktürk, Kristina Bowyer, Laurence Mignon, Sasidhar Pasupuleti, Daniel G. Glaze, Bernhard Suter, and Davut Pehlivan. 2022. "Assessing the burden on caregivers of MECP2 duplication syndrome." *Pediatric Neurology* 133: 1–8.
<https://doi.org/10.1016/j.pediatrneurol.2022.05.008>.

Assessing the Burden on Caregivers of *MECP2* Duplication Syndrome

Muharrem Ak, MD ^a, Zekeriya Akturk, MD ^b, Kristina Bowyer, LPN ^c,
Laurence Mignon, PhD ^c, Sasidhar Pasupuleti, MS ^d, Daniel G. Glaze, MD ^{a, e},
Bernhard Suter, MD ^{a, e}, Davut Pehlivan, MD ^{a, e, *}

^a Section of Pediatric Neurology and Developmental Neuroscience, Department of Pediatrics, Baylor College of Medicine, Houston, Texas

^b Institute of General Practice and Health Services Research, School of Medicine, Technical University of Munich, Munich, Germany

^c IONIS Pharmaceuticals, Carlsbad, California

^d Bioinformatics Core, Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Houston, Texas

^e Blue Bird Circle Rett Center, Texas Children's Hospital, Houston, Texas

Introduction

The *MECP2* gene, encoding methyl CpG binding protein 2 (MeCP2), is located at Xq28 region of the X chromosome. Loss-of-function or deletion mutations of *MECP2* are known to be causative for Rett syndrome (RTT, MIM# 312750).¹ RTT, primarily affecting girls with an incidence of 1 in 10,000 to 15,000,² is a severe neurodevelopmental disorder (NDD) characterized by

developmental regression followed by developmental delay, growth failure, dysautonomia, functional gastrointestinal abnormalities (e.g. reflux, constipation, bloating), sleep disturbances, and hand stereotypies.³

In contrast, duplication or triplication of *MECP2* is known to cause MECP2 duplication syndrome (MDS, MIM #300260).^{4,5} The clinical presentation is variable, but there are several prevalent features (i.e., present in >50% of subjects) including infantile hypotonia, severe developmental delay, frequent respiratory infections, and epilepsy.⁶⁻¹³ Most people with MDS die in their 20s to 30s.^{7,13,14} The prevalence of MDS has not been fully explored; however, it has been reported as 1 in 100,000 live male births in Australia.¹⁵ Given that RTT is a relatively common and well-studied disorder, several studies have investigated the genotype-phenotype association and caregiver burden, and there are

Declaration of Interests: B.S. and D.P. receive funding support from Ionis Pharmaceuticals. K.B. and L.M. are employees of Ionis Pharmaceuticals and own Ionis stocks. Other authors declare no conflict of interest related to this work.

* Communications should be addressed to: Dr. Pehlivan; 6701 Fannin Street Suite 1250; Houston, TX 77030.

E-mail address: pehlivan@bcm.edu (D. Pehlivan).

RTT-specific outcome measures. On the other hand, MDS is much less studied and there are no MDS-specific outcome measures or caregiver burden studies.

Caregiving is a natural piece of parenting; however, this evolves into an increasingly difficult and multilayered task when a child has or develops physical and/or mental limitations. The challenges faced by the caregivers, including the unmet need for psychological and emotional support, have been widely studied for chronic diseases.¹⁶⁻¹⁸ The task of caring for a child with complex disabilities, resulting from a rare disease, can be very arduous for caregivers, primarily due to debilitating disease progression and the lack of resources. It has been shown that the burden of caring for a child with an NDD involves the parents' self-perceived stress on their daily functioning such as relationship with other family members, quality of life, and physical, mental, and economic well-being.¹⁹⁻²³ Some families cope well with these challenges, whereas others are severely impacted by their child's disabilities and the demands of the disease. These differences result from multifaceted factors such as the life experiences and coping mechanisms of the child and their parents, the functioning and strength of the family unit, and the effectiveness of their support network including relatives, friends, and professional services. It is important to explore and address these concerns since caregiver's well-being can directly impact the well-being of the affected individual and eventually the society in general.

In this study, we investigated the critical components of the burden on caregivers of individuals with MDS by exploring the contribution of the most prevalent clinical features and factors leading to psychosocial burden. In addition, we developed and validated a burden of disease scale specific to MDS.

Material and Method

Patient registry and survey delivery

We created an online Health Insurance Portability and Accountability Act-compliant registry portal for families with MDS after institutional review board approval (H-46176) by Baylor College of Medicine. All caregivers provided a written consent form for their registration, participation in survey studies, and publication of the results. As part of the registration process, families have to upload their genetic report confirming the molecular diagnosis of MDS into the server. Thus, all subjects had an established genetic diagnosis before enrollment. Eligible subjects were invited to participate in the study through e-mail they provided in the portal, and the study is advertised in family organizations' social media accounts. The survey was developed at eighth grade reading level and provided in English. All the collected data were stored in password-protected Baylor College of Medicine and Texas Children's Hospital secured computers.

The study was designed as a cross-sectional study involving the caregivers of individuals with MDS. A caregiver was defined as a family member or other person who primarily cared for the affected individual. Only one caregiver was allowed to take the survey. The duration of caregiving was not limited to a certain period to encompass the range of caregiver burden.

Development of caregiver burden survey

The survey was developed by the MDS clinicians (authors D.P., D.G., and B.S.) at the Blue Bird Circle Rett Center at Texas Children's Hospital and experts on survey development (authors L.M. and K.B.) and computer programmer (author S.P.). The first section focused on demographic features of the caregiver such as age, race, and ethnicity; diagnosis process (e.g., how many providers they

saw until establishing the diagnosis, how many genetic tests were run, first presenting symptoms); and treatment-related questions (e.g., type and frequency of therapies, difficulties identifying medical professionals familiar with MDS in their area, visiting large referral center). The second section included questions about the support that caregivers were receiving while taking care of the individual with MDS (e.g., school/day care duration and satisfaction, support from family/friend/spouse) and queried the caregivers about their level of anxiety, depression, and emotional exhaustion using a Likert scale (none, mild, moderate, severe). After the survey underwent several rounds of revisions by the coauthors, the finalized version was reviewed by two independent parents to confirm the relevance of each item and ascertain the wording of the questions was adequate. The online survey was available to parents between September 1, 2020, and November 30, 2020.

In addition to the structured questions, we asked two open-ended questions to allow families to describe their challenges freely. These included "Please describe how taking care of an MDS individual affects your mental health" and "Please explain what other challenges you are facing not mentioned above as a caregiver." For the open-ended questions, two MDS experts (authors D.P. and B.S.) categorized parental concerns in different subgroups based on caregivers' answers.

Statistical methods and burden scale development

We used descriptive statistics including frequency and percentages for sociodemographic variables and clinical features. We applied the Pearson chi-square test for the categorical variables and performed a posthoc Tukey test to investigate the statistical differences across races. We used Spearman correlation to explore the relationships between the ages of individuals with MDS and their caregivers, and the total burden score (TBS).

Burden scale development

Team of experts from various backgrounds (patient advocacy, patient-centric scale development, and physicians familiar with MDS clinical features) developed the burden scale items after multiple rounds of meetings to investigate the caregivers' relationship with other family members/spouses, quality of life, and physical, mental, and economic well-being. Scale items were purposefully designed to be brief and concise while at the same time comprehensively covering the overall burden of caregivers. All experts agreed on a six-item burden scale. For each question, a three-point Likert scale (mild, moderate, and severe) was used.

The burden scale underwent validity, reliability, and exploratory factor analysis procedures. The Cronbach alpha coefficient was used to calculate the internal validity and reliability of the scale. Principal component analysis was used to determine the factor structure of the scale. For the sampling adequacy, we used the Kaiser-Meyer-Olkin measure. Also, we used a Scree plot to evaluate factor structure. To assess the similarity between independent variables in the burden scale, we checked for multicollinearity between the items. We finally ran a total variance test for the burden scale.

We used IBM SPSS Statistics for Macintosh, Version 28.0. Armonk, NY: IBM Corp for all statistical analyses.

Results

Participants' demographics

A total of 237 surveys were completed. We excluded 111 surveys due to duplicate submissions (the reminder announcements through the social media and e-mails let them resubmit the same

form multiple times since the families assumed that the initial submission was not successful). Of the remaining 126, 18 surveys were excluded due to an inability to confirm the diagnosis because of a missing genetic report and seven surveys were excluded because the individuals with MDS were female and therefore did not show the classical spectrum of the disease. The final analysis presented in this article was performed on 101 surveys. [Figure 1](#) shows all inclusion/exclusion steps in detail. Of note, the surveys belonging to the parents of three female patients were included since they had a translocation to an autosomal chromosome, and thus presented with classic MDS due to selective X-inactivation.

Seventy-six caregiver participants were Caucasians, seven Asians, nine Hispanics, two African Americans, and seven mixed background ([Table 1](#)). The ages of the individuals with MDS ranged from 1 month to 51 years with the following distribution; zero to five years: 38.6%, six to 11 years: 32.7%, 12 to 17 years: 12.9%, and 18 years and above: 15.8%. The age of the caregivers was categorized into three age groups: 21 to 33 years: 19.8%, 34 to 43 years: 49.5%, and 44 years and above: 30.7% ([Table 1](#)). Eighty-eight of the caregivers who completed the survey were mothers. Details of the demographics are summarized in [Table 1](#).

Diagnosis and treatment-related questions and satisfaction of caregiver

We also investigated health resources, challenges in diagnosis, and access to MDS experts. A total of 69.3% of the individuals with MDS attended day care or school with an average hour of attendance of 26.50 hours per week ([Table 2](#)). Of the caregivers, 41.6% were either satisfied or very satisfied with the day care/school.

All caregivers reported receiving support from a partner/spouse, family members, friends, or others (e.g., paid caregivers and home nursing). A total of 37 caregivers reported receiving support only from a partner/spouse, whereas 21 caregivers received support from all three groups (partner/spouse, family, and friends). Overall, 63% (58 of 91 of respondents) described themselves as satisfied or very satisfied with the support they were receiving from their community.

Of the respondents, 85 (84.1%) caregivers reported difficulties in accessing medical professionals familiar with MDS in their area and 52 (51.5%) of them had their child with MDS evaluated once a year in a center of excellence or large tertiary center. A total of 90 caregivers (89.1%) reported that their children with MDS were

TABLE 1
Demographics of Individuals With MDS and Their Caregivers

	Number	Percent
Ethnicity of the MDS individual		
White	76	75.2
Asian	7	6.9
Mixed races	7	6.9
Hispanic or Latino	9	8.9
African American	2	2
Age of MDS individual (years)		
0-5	39	38.6
6-11	33	32.7
12-17	13	12.9
18 and above	16	15.8
Country		
United States	55	54.5
Canada	8	7.9
European countries	24	23.8
Australia	7	6.9
Japan	4	4
Brazil	1	1
Puerto Rico	1	1
Argentina	1	1
Primary caregiver		
Mother	88	87.9
Father	12	10.1
Sister	1	2
Age of caregiver		
21-33	20	19.8
34-43	50	49.5
44 and above	31	30.7

Abbreviation:

MDS = MECP2 duplication syndrome

receiving some type of therapy. Only 22% of caregivers were receiving home-health nursing services. Additional details of health resources are provided in [Table 2](#).

We additionally investigated the burden on caregivers related to a potential delay in genetic diagnosis, number of genetic tests (exhaustion from multiple genetic tests with no definite diagnosis), and presenting symptoms of MDS. The average age of diagnosis was 23.3 months, ranging from a few weeks of life to 18 years. A genetic diagnosis was determined in 47.7% between 0 and 12 months, 28.8% between 13 and 24 months, and 23.5% at 25 months or later. Regarding the number of genetic testing, 47.5% were diagnosed after the first genetic test, 23.8% had two genetic tests, and 28.7% of

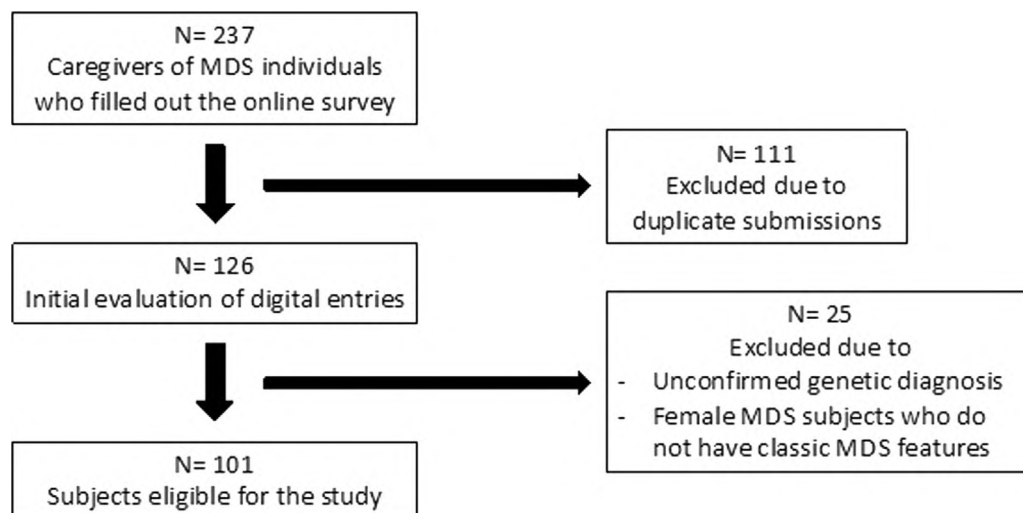


FIGURE 1. Flowchart of MD burden survey's cohort selection. MDS: MECP2 duplication syndrome.

TABLE 2
Diagnosis and Treatment-Related Questions

	Number	%
Do you have difficulty identifying medical professionals familiar with MDS in your area?		
Yes	85	84.2
No	16	15.8
Does your child receive home-health nursing services?		
Yes	23	22.8
No	78	77.2
Does your child go to day care/school		
Yes	70	69.9
No	31	30.1
Visiting a center of excellence or large referral center		
Yes	52	52.0
No	48	48.0
Who supports you while taking care of the patient		
Partner/spouse	37	36.6
Partner/spouse/family	18	17.8
Family	7	6.9
Partner/spouse/family/friend	19	18.9
Partner/spouse/family/nanny/home nursing/paid caregivers, nurse	20	19.8
Type of therapies		
Physical therapy, occupational therapy, speech therapy	32	31.68
Physical therapy, occupational therapy, speech therapy, and additional therapy	32	31.68
Physical therapy alone or in combination with at least one of the following: speech therapy, hippotherapy, aqua, occupational, ABA therapy	15	14.85
Speech therapy alone or in combination with occupational therapy with	6	5.95
Music and massage	1	0.99
No therapy	15	14.85
Number of genetic tests until the final diagnosis was reached		
One genetic testing	49	48.51
Two genetic testing	24	23.76
Three or more genetic testing	28	27.72

Abbreviations:

ABA = Applied behavioral analysis

MDS = MECP2 duplication syndrome

the individuals underwent three or more genetic tests to establish the final diagnosis.

Caregivers' self-perceived burden

To better understand the burden of caregiver, we asked about their self-reported feelings of anxiety due to the expected shortened life span of individuals with MDS, and the impact on the relationship with spouse and/or family members, social life, personal health, job and personal aspirations, and financial well-being. A Likert scale ranging from mildly affected to severely affected was used to assess these domains.

For the internal validity of the scale, the Cronbach alpha value was 0.801 for these six items, which confirms the validity of our scale (minimally accepted Cronbach alpha value is 0.7). The Kaiser-Meyer-Olkin measure of sampling adequacy value for the six-item scale was 0.820, which confirms the adequacy of sampling in our

study. Furthermore, the factor load describing the variability between items in the scale was between 0.486 and 0.780 (Table 3), which is within the acceptable range. No multicollinearity was found among the scale items. As a result, a factor structure consisting of six items and a single dimension, which could explain 50.7% of the total variance, was obtained (Fig 2). TBS was calculated by summing item scores, with a minimum value of 7 to a maximum value of 24, and higher scores indicating a more severe burden. Mean TBS was 17.8 ± 4.0 (median: 18.0, minimum 7, maximum 24). We further divided the total score into three equal categories to classify mild, moderate, and severe as 7 to 12: mild, 13 to 18: moderate, and 19 to 24: severely affected for the convenience of statistical analysis.

There was a significant association between races and burden scores. Hispanic caregivers had a higher burden score compared with Caucasian caregivers (P value: 0.03). No difference in burden score was found between Caucasians, and African

TABLE 3
Component Matrix*

	Component 1
1. How anxious are you about the progression of the syndrome including a potentially shortened life span?	0.486
2. Does taking care of an MDS individual affect your relationship with your spouse or other family members?	0.747
3. Does taking care of an MDS individual affect your social life (such as going out with spouse/friends, taking vacations)?	0.780
4. Does taking care of an MDS individual affect your personal health (e.g., lack of sleep, preventing from exercise)?	0.712
5. Does taking care of an MDS individual affect job and personal aspirations?	0.768
6. Does taking care of an MDS individual affect your financial well-being?	0.738

Abbreviation:

MDS = MECP2 duplication syndrome

Extraction method: Principal component analysis.

* One component extracted.

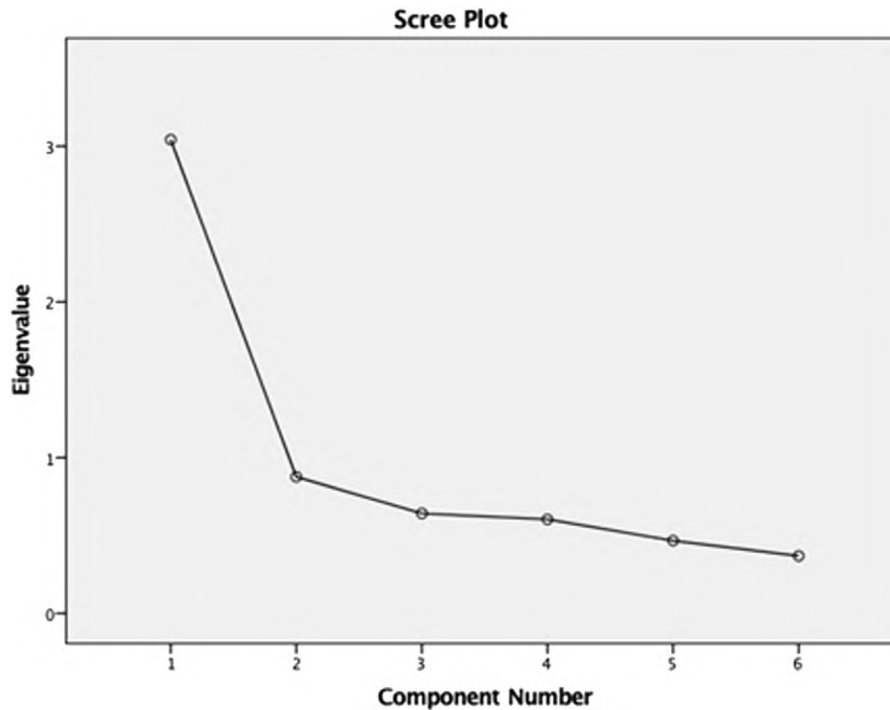


FIGURE 2. Scree plot for the parental burden scale representing the eigenvalues and the proportion of variance accounted for by the principal components.

Americans (P value: 1.00), Asians (P value: 0.945), and mixed races (P value: 0.777). We did not observe a burden difference based on the countries of caregivers (P value: 0.643).

Regarding MDS symptoms, we detected a statistically significant association between parental burden score and epilepsy. Caregivers of individuals with MDS with epilepsy ($n = 58$) had a higher burden score compared with caregivers of individuals with MDS without epilepsy ($n = 43$, $P = 0.021$). However, we did not find any statistical differences between the TBS, and constipation ($P = 0.147$), ambulatory status ($P = 0.395$), or infection ($P = 0.444$) (Table 4). No correlation was found between the TBS and age of the patient ($r = -0.010$, $P = 0.290$), age of caregiver ($r = -0.025$, $P = 0.805$), or duration of care ($r = -0.111$, $P = 0.267$).

The caregivers' self-perceived degree of anxiety was reported as not affected (17.8%, $n = 18$), mildly affected (25.7%, $n = 26$), moderately affected (32.6%, $n = 33$), and severely affected (23.7%, $n = 24$) and showed a significant difference ($P = 0.029$) between the TBS and these categories. The degree of self-perceived depression in caregivers was reported as not affected, mildly affected, moderately affected, and severely affected in 30.6% ($n = 31$), 38.6% ($n = 39$), 20.7% ($n = 21$), and 9.9% ($n = 10$), respectively. There was a statistically significant association between depression and TBS ($P = 0.007$). A similar significance was detected between caregivers' self-perceived emotional exhaustion (not affected [11.8%, $n = 12$], mildly affected [16.8%, $n = 17$], moderately affected [35.6%, $n = 36$], and severely affected [35.6%, $n = 36$]) and burden score ($P = 0.004$) (Table 5).

No association was found between TBS and day care/school attendance ($P = 0.137$), number of days per week in day care/school ($P = 0.350$), therapy frequency (P value: 0.138), visiting a center of excellence ($P = 0.264$), or receiving home health services ($P = 0.381$).

Open-ended questions

In addition to the structured questions, we asked two open-ended questions to the caregivers to freely describe their feelings on their mental health and one open-ended question to identify

additional challenges that caregivers were experiencing. Twenty caregivers provided additional concerns for the open-ended mental health question; the most common ones included self-described posttraumatic stress disorder (four individuals), physical exhaustion (four individuals), and lack of sleep (two individuals). Forty-three caregivers filled the "other challenges" open-ended burden question. Two of the authors (B.S. and D.P.) categorized these responses into four domains. The most common challenges among caregivers included insurance and financial challenges, difficulties in accessing experts and appropriate treatment, shortened life expectancy, and challenges with the spouse/family members. We have provided a summary of these concerns in the Supplemental Table. Two such responses are provided below to exemplify the opposite spectrum (burned out versus resilience) of burden experienced by caregivers:

"Another challenge we face is help. Taking care of a child with severe issues, no one is comfortable or willing to watch your child. We have no date nights, no vacations, no family picnics, no holidays. We have to take turns doing things. Having a severely disabled child affects our relationship in so many ways. Our family is constantly split apart as it is very difficult to do anything together in the community ..."

"It's exhausting but I will do whatever it takes to care for my child. I only wish I could take the pain and illness from him and want him to live the best life possible. I may feel worn down and some days I'm not sure how I keep going but I will never give up or let him down..."

Discussion

In this study, we conducted the first burden survey on caregivers of individuals with MDS through our registry. We developed a validated six-item, single-dimension burden scale to assess the burden on caregivers. A positive association between the TBS, and

TABLE 4
Comparison of Burden Scores With MDS Features

	Categorized Burden Score						Chi-square	P Value
	Mild		Moderate		Severe			
	n	%	n	%	n	%		
Epilepsy								
Yes	12	20.7	19	32.8	27	46.6	7.705	0.021
No	10	23.3	24	55.8	9	20.9		
Ambulatory status							1.856	0.395
Ambulatory	11	28.9	15	39.5	12	31.6		
Nonambulatory	11	17.5	28	44.4	24	38.1		
Frequent infections							1.622	0.444
Yes	11	19.6	22	39.3	23	41.1		
No	11	24.4	21	46.7	13	28.9		
Constipation							6.803	0.147
Never, rare	7	46.7	5	33.3	3	20.0		
Sometimes	5	20.8	10	41.7	9	37.5		
Often, always	10	16.1	28	45.2	24	38.7		

Abbreviation:
MDS = MECP2 duplication syndrome

self-reported anxiety, depression, and emotional exhaustion was found. From the MDS physical symptoms, epilepsy was contributing to parental burden. A higher caregiver burden on Hispanics compared with Caucasians was identified.

The caregiver burden on various NDDs has been extensively studied. Eom et al. found that 65% of mothers have significant levels of stress and depression in pediatric mitochondrial disease.²⁴ The potential causes of increased parental burden include excessive demand in care, limited daily functioning of the child, and limited interaction between child and parent. Maridal et al. studied the psychological distress among 63 caregivers of NDD in rural Nepal and detected a high level of distress in caregivers of individuals with NDD (46%).²⁵ The authors further identified that a majority of the caregivers reported a negative effect on the caregiver's economy (70%), physical health (65%), social life (64%), and dreams and expectations for the future (81%). Caregiver burden is well studied in RTT, an allelic disorder of MDS.^{20,22,23,26-31} Laurvick et al. investigated factors that have a role in the physical and mental health of mothers of children with RTT.³⁰ The authors identified several factors, including the mothers working full-time or part-time outside the home, having some high school education, having private health insurance, the child not having breathing problems in the last two years, and the child not having home-based structured therapy as contributing positively to the physical and mental health of mothers. Sarajlija et al. conducted a questionnaire study on 49 mothers of individuals with RTT from Serbia to assess health-related quality of life and observed severe depression in 15 (30.6%) of the participants.³² Our study identified moderate to severe self-perceived depression in 31% of caregivers. Our study further identified a positive correlation between depression and burden score. Cianfaglione et al. studied 87 mothers of individuals with RTT and found elevated levels of anxiety compared with British normative data for women.³³ Moderate to severe self-perceived anxiety was observed in 57% of our caregivers, which correlated with a higher burden score. In addition to the correlation between burden, and depression and anxiety, our study further found an association between self-perceived emotional exhaustion and burden score in MDS caregivers. Pari et al. investigated the parental stress level in 79 Italian caregivers of RTT and detected significant stress levels in about 39% of the fathers, compared with 44% of the mothers. In our study, most of the caregivers were mothers (88 vs 12), however; no difference was observed between the mothers and fathers in burden scores. Although there are significant differences between health care systems in participating caregivers' countries in our

study, we did not find any statistical difference in burden scores between individuals from different countries.

Some physical symptoms of individuals with MDS can have more impact on the burden of caregivers. Mori et al. comprehensively investigated the factors contributing to the physical and emotional well-being of parents of individuals with RTT.²⁷ Authors identified that individuals with RTT having frequent sleep disturbances contribute to the poorer physical well-being of parents. In this study, whereas sleep has not been determined as a big issue in individuals with MDS, epilepsy has been identified as an important physical symptom that contributes to the burden of MDS caregivers. Byiers et al. studied the potential factors contributing to parental stress of 35 girls and women with RTT. Interestingly, seizure and gastrointestinal pain were the only two factors correlated with parental stress.³⁴ Epilepsy is common in *MECP2*- and Rett-related disorders, including RTT, MDS, and *CDKL5* deficiency disorder.^{11,35-37} Vignoli et al. studied the electroencephalography and seizure characteristics of eight individuals with MDS and identified the presence of epilepsy in 90% of adolescent subjects.¹⁰ Later on, Marafi and Suter et al. showed that developmental regression coincides with the onset of epilepsy.¹¹ In our unpublished cohort of 85 subjects with MDS, we found that epilepsy is a dynamic clinical feature that becomes almost universal after age 15 years (95%) and epilepsy is the major risk factor leading to regression and death in individuals with MDS.

Our study also identified higher TBS in Hispanic caregivers compared with Caucasians. Several studies report racial/ethnic disparities in disease burden especially comparing Hispanics and Caucasians.³⁸⁻⁴⁰ Potential explanations for this disparity include received quality of care⁴¹; quality of provider-caregiver interaction⁴²; failure to seek out services for a variety of reasons, including language barriers and lack of access to resources that can direct caregivers to the appropriate providers; and fear surrounding their immigration status.⁴³ We did not find any country-based difference in parental burden score.

No correlation was found between the TBS and duration of care, age of the individual with MDS, and age of the caregiver. There are conflicting results about the impact of age and duration of care in the literature. Lounds et al. studied the longitudinal effect on maternal well-being of autistic mothers.⁴⁴ The authors identified an improvement in the maternal well-being and quality of the mother-child relationship. This improvement was linked to declining behavioral problems due to the prescription of more psychotropic medications and exiting from high school during the

TABLE 5
TBS in Relation to Anxiety, Depression, and Emotional Exhaustion*

	Mild	Moderate	Severe	Test
Anxiety				
Mildly affects: Number; %	8; 30.8%	11; 42.3%	7; 26.9%	$\chi^2 = 10.831$ $P = 0.029$
TBS	57.1%	29.7%	21.9%	
Moderately affects: Number; %	6; 18.2%	16; 48.5%	11; 33.3%	
TBS	42.9%	43.2%	34.4%	
Severely affects: Number; %	0; 0.0%	10; 41.7%	14; 58.3%	
TBS	0.0%	27.0%	43.8%	
Depression				
Mildly affects: Number; %	10; 25.6%	18; 46.2%	11; 28.2%	$\chi^2 = 14.208$ $P = 0.007$
TBS	83.3%	62.1%	37.9%	
Moderately affects: Number; %	2; 9.5%	10; 47.6%	9; 42.9%	
TBS	16.7%	34.5%	31.0%	
Severely affects: Number; %	0; 0.0%	1; 10.0%	9; 90.0%	
TBS	0.0%	3.4%	31.0%	
Emotional exhaustion				
Mildly affects: Number; %	7; 41.2%	7; 41.2%	3; 17.6%	$\chi^2 = 15.506$ $P = 0.004$
TBS	43.8%	17.9%	8.8%	
Moderately affects: Number; %	8; 22.2%	17; 47.2%	11; 30.6%	
TBS	50.0%	43.6%	32.4%	
Severely affects: Number; %	1; 2.8%	15; 41.7%	20; 55.6%	
TBS	6.3%	38.5%	58.8%	

Abbreviation:

TBS = Total burden score

* Anxiety, depression, and emotional exhaustion were divided into three categories as mild, moderate, and severe. Total number of respondents was provided in number and percentage. χ^2 test is used to analyze the relationship with TBS.

study period. Sloan et al. investigated the longitudinal effects on the well-being of parents of children with developmental or mental health problems in a large cohort (N = 1101).⁴⁵ Although a longer duration of the child's condition had adverse effects on parental well-being, the current age of the parent did not negatively impact well-being.

Open-ended questions

We additionally created a section to allow parents to freely express their feelings and challenges during their long journey. We summarized these challenges under four categories (Table S1). Several families reported significant challenges with insurance processes including insurance coverage and getting approvals for therapies considered to be the mainstream management of NDDs. Caregivers also expressed challenges resulting from society's lack of awareness and society's prejudiced behavior toward developmental disorders. Reproductivity was another challenge we did not consider as an issue previously before this study. Three-quarter of children with MDS were born to carrier mothers, meaning that the chance of having another male child with MDS was 50% for future pregnancies; this could add complexity and burden to families since they may need/want to consider *in vitro* fertilization for future family planning, which could bring different challenges to these families.

Our study identified several factors that can contribute to the parental burden, including clinical problems (seizure), psychosocial environment (e.g., bias in the society toward NDDs), and challenges with insurance and financial issues. Although we attempted to single out specific symptoms/domains, we are considering that all these circumstances contribute to parental burden. On the other hand, support from partner/spouse, family, and friends is an important asset to the caregivers, which might potentially alleviate the burden (of note, although 63% of caregivers were either satisfied or very satisfied with the support they are receiving from their environment, this support does not improve caregivers' burden).

The limitations of the study included the following: (1) the study was conducted as a cross-sectional study over two-month period;

(2) families probably reported the burden over the last few months, thus this may not reflect the overall burden on caregivers longitudinally; and (3) the great majority of our participants were from North America and Europe, thus results may be confined to the cultural and socioeconomic status of these countries. In addition, this study was conducted during the coronavirus disease 2019 pandemic, which might have increased the stress on families.

In this study, we conducted the first burden survey on caregivers with individuals with MDS and explored the potential contributors to parental burden. Using our newly developed, reliable, and valid burden scale, we identified a higher parental burden associated with MDS clinical features (epilepsy) as well as self-perceived anxiety, depression, and emotional exhaustion. Addressing caregivers' burden could not only improve the health of this vulnerable patient population, but it would also improve the quality of life of their families, which would be a benefit to society as a whole.

Acknowledgments

We thank all families for their participation in this research. This study was supported by the MECP2 Duplication Foundation. D.P. is supported by International Rett Syndrome Foundation (IRSF grant #3701-1), and B.S. and D.G.G. are supported by Blue Bird Circle Foundation. The MECP2 Duplication Foundation funded the establishment and maintenance of the online MDS server. S.P. and M.A. receive salary support from MECP2 Duplication Foundation.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pediatrneurol.2022.05.008>.

References

- Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet.* 1999;23:185–188.
- Hagberg B. Rett's syndrome: prevalence and impact on progressive severe mental retardation in girls. *Acta Paediatr Scand.* 1985;74:405–408.

3. Sandweiss AJ, Brandt VL, Zoghbi HY. Advances in understanding of Rett syndrome and MECP2 duplication syndrome: prospects for future therapies. *Lancet Neurol*. 2020;19:689–698.
4. Meins M, Lehmann J, Gerresheim F, et al. Submicroscopic duplication in Xq28 causes increased expression of the MECP2 gene in a boy with severe mental retardation and features of Rett syndrome. *J Med Genet*. 2005;42:e12.
5. Van Esch H, Batters M, Ignatius J, et al. Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. *Am J Hum Genet*. 2005;77:442–453.
6. Ramocki MB, Tavayev YJ, Peters SU. The MECP2 duplication syndrome. *Am J Med Genet A*. 2010;152A:1079–1088.
7. Miguet M, Faivre L, Amiel J, et al. Further delineation of the MECP2 duplication syndrome phenotype in 59 French male patients, with a particular focus on morphological and neurological features. *J Med Genet*. 2018;55:359–371.
8. Van Esch H. MECP2 duplication syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*(R). Seattle, WA: University of Washington, Seattle; 1993–2022.
9. Lim Z, Downs J, Wong K, Ellaway C, Leonard H. Expanding the clinical picture of the MECP2 Duplication syndrome. *Clin Genet*. 2017;91:557–563.
10. Vignoli A, Borgatti R, Peron A, et al. Electroclinical pattern in MECP2 duplication syndrome: eight new reported cases and review of literature. *Epilepsia*. 2012;53:1146–1155.
11. Marafi D, Suter B, Schultz R, Glaze D, Pavlik VN, Goldman AM. Spectrum and time course of epilepsy and the associated cognitive decline in MECP2 duplication syndrome. *Neurology*. 2019;92:e108–e114.
12. Pascual-Alonso A, Blasco L, Vidal S, et al. Molecular characterization of Spanish patients with MECP2 duplication syndrome. *Clin Genet*. 2020;97:610–620.
13. Peters SU, Fu C, Suter B, et al. Characterizing the phenotypic effect of Xq28 duplication size in MECP2 duplication syndrome. *Clin Genet*. 2019;95:575–581.
14. Van Esch H. MECP2 duplication syndrome. *Mol Syndromol*. 2012;2:128–136.
15. Giudice-Nairn P, Downs J, Wong K, et al. The incidence, prevalence and clinical features of MECP2 duplication syndrome in Australian children. *J Paediatr Child Health*. 2019;55:1315–1322.
16. Liedgens H, Obradovic M, De Courcy J, Holbrook T, Jakubanis R. A burden of illness study for neuropathic pain in Europe. *Clinicoecon Outcomes Res*. 2016;8:113–126.
17. Ozdemir Koyu H, Tas Arslan F. The effect of physical and psychosocial symptoms on caregiver burden of parents of children with cancer. *Eur J Cancer Care (Engl)*. 2021;30, e13513.
18. Zhukovsky DS, Rozmus CL, Robert R, Bruera E, Wells RJ, Cohen MZ. Symptom and illness experience for English and Spanish-speaking children with advanced cancer: child and parent perspective. *Children (Basel)*. 2021;8:657.
19. Iosif AM, Sciolla AF, Brahmabhatt K, Seritan AL. Caregiver burden in fragile X families. *Curr Psychiatry Rev*. 2013;9:85–91.
20. Pari E, Cozzi F, Rodocanachi Roidi ML, Grange F, Toshimori K, Ripamonti E. Parenting girls with Rett syndrome: an investigation on self-perceived levels of stress. *J Appl Res Intellect Disabil*. 2020;33:1348–1356.
21. Lach LM, Kohen DE, Garner RE, et al. The health and psychosocial functioning of caregivers of children with neurodevelopmental disorders. *Disabil Rehabil*. 2009;31:607–618.
22. Abbeduto L, Seltzer MM, Shattuck P, Krauss MW, Orsmond G, Murphy MM. Psychological well-being and coping in mothers of youths with autism, Down syndrome, or fragile X syndrome. *Am J Ment Retard*. 2004;109:237–254.
23. Griffith GM, Hastings RP, Oliver C, et al. Psychological well-being in parents of children with Angelman, Cornelia de Lange and Cri du Chat syndromes. *J Intellect Disabil Res*. 2011;55:397–410.
24. Eom S, Lee YM. Preliminary study of neurodevelopmental outcomes and parenting stress in pediatric mitochondrial disease. *Pediatr Neurol*. 2017;71:43–49.e1.
25. Maridal HK, Bjorgaas HM, Hagen K, et al. Psychological distress among caregivers of children with neurodevelopmental disorders in Nepal. *Int J Environ Res Public Health*. 2021;18:2460.
26. Lane JB, Salter AR, Jones NE, et al. Assessment of caregiver inventory for Rett syndrome. *J Autism Dev Disord*. 2017;47:1102–1112.
27. Mori Y, Downs J, Wong K, Leonard H. Longitudinal effects of caregiving on parental well-being: the example of Rett syndrome, a severe neurological disorder. *Eur Child Adolesc Psychiatry*. 2019;28:505–520.
28. Mori Y, Downs J, Wong K, Heyworth J, Leonard H. Comparing parental well-being and its determinants across three different genetic disorders causing intellectual disability. *J Autism Dev Disord*. 2018;48:1651–1665.
29. Mori Y, Downs J, Wong K, Anderson B, Epstein A, Leonard H. Impacts of caring for a child with the CDKL5 disorder on parental wellbeing and family quality of life. *Orphanet J Rare Dis*. 2017;12:16.
30. Laurvick CL, Msall ME, Silburn S, Bower C, de Klerk N, Leonard H. Physical and mental health of mothers caring for a child with Rett syndrome. *Pediatrics*. 2006;118:e1152–e1164.
31. Esbensen AJ, Seltzer MM. Accounting for the Down syndrome advantage? *Am J Intellect Dev Disabil*. 2011;116:3–15.
32. Sarajlija A, Djuric M, Tepavcevic DK. Health-related quality of life and depression in Rett syndrome caregivers. *Vojnosanit Pregl*. 2013;70:842–847.
33. Cianfaglione R, Hastings RP, Felce D, Clarke A, Kerr MP. Psychological well-being of mothers and siblings in families of girls and women with Rett syndrome. *J Autism Dev Disord*. 2015;45:2939–2946.
34. Byiers BJ, Tervo RC, Feyma TJ, Symons FJ. Seizures and pain uncertainty associated with parenting stress and Rett syndrome. *J Child Neurol*. 2014;29:526–529.
35. Tarquinio DC, Hou W, Berg A, et al. Longitudinal course of epilepsy in Rett syndrome and related disorders. *Brain*. 2017;140:306–318.
36. Demarest S, Pestana-Knight EM, Olson HE, et al. Severity assessment in CDKL5 deficiency disorder. *Pediatr Neurol*. 2019;97:38–42.
37. McKeon TA, Gaffield W. Viewing stereopictures in three dimensions with naked eyes. *Trends Biochem Sci*. 1990;15:412–413.
38. Benevides TW, Lee J, Nwosu NAO, Franks J. Understanding the family impact of autism spectrum disorder in a racially and ethnically diverse sample: findings from the National Survey of Children with Special Health Care Needs. *Matern Child Health J*. 2019;23:951–960.
39. Magana S, Smith MJ. Psychological distress and well-being of Latina and non-Latina White mothers of youth with an autism spectrum disorder: cultural attitudes towards coresidence status. *Am J Orthopsychiatry*. 2006;76:346–357.
40. Calderón V, Tennstedt SL. Ethnic differences in the expression of caregiver burden: results of a qualitative study. *J Gerontol Soc Work*. 1998;30:159–178.
41. Magana S, Parish SL, Rose RA, Timberlake M, Swaine JG. Racial and ethnic disparities in quality of health care among children with autism and other developmental disabilities. *Intellect Dev Disabil*. 2012;50:287–299.
42. Parish S, Magana S, Rose R, Timberlake M, Swaine JG. Health care of Latino children with autism and other developmental disabilities: quality of provider interaction mediates utilization. *Am J Intellect Dev Disabil*. 2012;117:304–315.
43. Magana S, Lopez K, Aguinaga A, Morton H. Access to diagnosis and treatment services among latino children with autism spectrum disorders. *Intellect Dev Disabil*. 2013;51:141–153.
44. Lounds J, Seltzer MM, Greenberg JS, Shattuck PT. Transition and change in adolescents and young adults with autism: longitudinal effects on maternal well-being. *Am J Ment Retard*. 2007;112:401–417.
45. Sloan CJ, Mailick MR, Hong J, Ha JH, Greenberg JS, Almeida DM. Longitudinal changes in well-being of parents of individuals with developmental or mental health problems. *Soc Sci Med*. 2020;264:113309.