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Authors

Killian, John T
Lane, Jane B
Lee, Hye-Seung
et al.

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Original Article

Caretaker Quality of Life in Rett Syndrome: Disorder Features and Psychological Predictors

John T. Killian Jr. MA [a], Jane B. Lane RN, BSN [b], Hye-Seung Lee PhD [c], James H. Pelham BS [a], Steve A. Skinner MD [d], Walter E. Kaufmann MD [e], Daniel G. Glaze MD [f], Jeffrey L. Neul MD, PhD [g], Alan K. Percy MD [b,*]

[a] *University of Alabama at Birmingham, School of Medicine, Birmingham, Alabama*
[b] *University of Alabama at Birmingham, Civitan International Research Center, Birmingham, Alabama*
[c] *Health Informatics Institute, Department of Pediatrics, Morsani College of Medicine, University of South Florida, Tampa, Florida*
[d] *Greenwood Genetic Center, Greenwood, South Carolina*
[e] *Boston Children's Hospital (Harvard), Boston, Massachusetts*
[f] *Baylor College of Medicine, Houston, Texas*
[g] *University of California San Diego, San Diego, California*

ABSTRACT

OBJECTIVE: Rett syndrome is a severe neurodevelopmental disorder affecting approximately one in 10,000 female births. The clinical features of Rett syndrome are known to impact both patients' and caretakers' quality of life in Rett syndrome. We hypothesized that more severe clinical features would negatively impact caretaker physical quality of life but would positively impact caretaker mental quality of life. **METHODS:** Participants were individuals enrolled in the Rett Natural History Study with a diagnosis of classic Rett syndrome. Demographic data, clinical disease features, caretaker quality of life, and measures of family function were assessed during clinic visits. The Optum SF-36v2 Health Survey was used to assess caretaker physical and mental quality of life (higher scores indicate better quality of life). Descriptive, univariate, and multivariate analyses were used to characterize relationships between child and caretaker characteristics and caretaker quality of life. **RESULTS:** Caretaker physical component scores (PCS) were higher than mental component scores (MCS): 52.8 (9.7) vs 44.5 (12.1). No differences were demonstrated between the baseline and 5-year follow-up. In univariate analyses, disease severity was associated with poorer PCS ($P = 0.006$) and improved MCS ($P = 0.003$). Feeding problems were associated with poorer PCS ($P = 0.007$) and poorer MCS ($P = 0.018$). In multivariate analyses, limitations in caretaker personal time and home conflict adversely affected PCS. Feeding problems adversely impacted MCS. **CONCLUSIONS:** Caretaker quality of life in Rett syndrome is similar to that for caretakers in other chronic diseases. Disease characteristics significantly impact quality of life, and feeding difficulties may represent an important

The authors report no conflicts.

Mr. J.T.K. is a medical student at the University of Alabama at Birmingham. Ms. J.B.L. is a paid consultant at Rettsyndrome.org regarding clinical matter related to Rett syndrome and is funded by NIH U54 grant HD061222. H.-S.L. is a statistician for the Rare Disease Clinical Research Network at the University of South Florida Data Management and Coordinating Center. Mr. J.H.P. is a medical student at the University of Alabama at Birmingham. Dr. S.A.S. serves on the Scientific Advisory Board of Rettsyndrome.org and is funded by NIH U54 grant HD061222. Dr. W.E.K. serves on the Scientific Advisory Board of Rettsyndrome.org, receives grant funding from Rettsyndrome.org for the IGF-1 clinical trial, and is funded by NIH U54 grant HD061222. Dr. D.G.G. serves on the Scientific Advisory Board of Rettsyndrome.org, is funded by NIH U54 grant HD061222 and the Blue Bird Circle in Houston for studies related to Rett syndrome, and was an investigator on the Neuren Pharmaceuticals clinical trial for Rett syndrome (NNZ-2566) which concluded in 2014. Dr. J.L.N. serves on the Scientific Advisory Board of Rettsyndrome.org, receives grant funding from Rettsyndrome.org for the research studies related to Rett syndrome, is funded by NIH U54 grant HD061222 of which he is the Administrative Leader, and was an investigator on the Neuren Pharmaceuticals clinical trial for Rett syndrome (NNZ-2566) which concluded in 2014. Dr. A.K.P. serves on the Scientific Advisory Board of Rettsyndrome.org, is the principal investigator of the Rare Diseases Clinical Research Center grant for Rett syndrome, MECP2 Duplication Disorder, and Rett-related Disorders grant, HD061222 (NICHD and NINDS), is funded by NIH U54 grant HD061222, receives administrative support from the Civitan International Research Center, and was an investigator on the Neuren Pharmaceuticals clinical trial for Rett syndrome (NNZ-2566) which concluded in 2014.

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* Communications should be addressed to: Dr. Percy; University of Alabama at Birmingham; Civitan International Research Center; 1720 2nd Avenue South; CIRC 320E; Birmingham, AL 35294.
E-mail address: apercy@uab.edu

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clinical target for improving both child and caretaker quality of life. The stability of quality-of-life scores between baseline and five years adds important value.

Keywords: Rett syndrome, *MECP2*, SF-36v2, ANCOVA, general linear model

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Introduction

Rett syndrome is a severe neurodevelopmental disorder occurring in about 1 of 10,000 female births, associated with *Methyl-CpG–binding protein 2* (*MECP2*) gene mutations in more than 95% of individuals with classic Rett syndrome.[1-3] Classic Rett syndrome criteria are partial or complete loss of purposeful hand skills and acquired spoken language, gait abnormalities, and hand stereotypies.[4] Quality of life (QOL) for patients and caregivers represents an important metric in outcomes-oriented health care delivery.[5,6] Rett syndrome impacts patients' physical and psychosocial quality of life, measured by the Child Health Questionnaire (CHQ),[7] and places unique demands on caregivers and families requiring additional consideration.

Two studies have examined caretaker quality of life in Rett syndrome, identifying characteristics that affect caretaker well-being.[8,9] In one, only 70.4% (n = 95) of children had an *MECP2* mutation.[8] It assessed clinical measures for Rett syndrome including *MECP2* mutation, epilepsy, musculoskeletal problems, fractures, breathing problems, sleeping problems, stereotyped behaviors, and movement, yet other manifestations including ambulation, feeding problems, and overall clinical severity were not assessed. More extensive analysis would empower clinicians to target specific disease features allowing the greatest benefit for caretaker well-being.

We identified characteristics of caretaker quality of life in Rett syndrome and determined key predictors from the National Institutes of Health–funded Natural History Study, analyzing relationships of caretaker quality of life with both caretaker and child disease–burden characteristics to address the following hypotheses: (1) caretaker physical and mental quality of life will be diminished relative to general population data and will be similar to other chronic diseases; (2) more severe clinical features will negatively impact caretaker physical quality of life but will positively impact mental quality of life; (3) caretaker characteristics will impact caretaker quality of life; and (4) caretaker quality of life will change over time similar to the general population.

Materials and Methods

Data collection

As part of the multicenter Rett Natural History Study (RNHS), individuals with classic Rett syndrome were recruited from 2006 to 2014 and evaluated as previously described.[10] An RNHS geneticist or neurologist (D.G.G., J.L.N., A.K.P., S.A.S., W.E.K.) confirmed the diagnosis of classic Rett syndrome using established diagnostic criteria.[4,11] *MECP2* testing was performed on all registrants by a qualified laboratory. Institutional review board approval was obtained at each study site. Families of participants granted informed assent because of inability of participants to understand the purposes of the protocol. The RNHS is registered as clinical trial NCT00296764.

SF-36v2 quality-of-life instrument

The Optum SF-36v2 Health Survey (SF-36v2) was designed to evaluate physical and mental health with higher scores representing better quality of life. It has been validated in a variety of settings ranging from clinical practice to population surveys, for both patients and caregivers.[12-16] The SF-36v2 assesses eight health domains: (1) physical functioning; (2) role limitations due to physical problems; (3) bodily pain; (4) general mental health; (5) role limitations due to emotional problems; (6) vitality; (7) social functioning; and (8) general health perceptions.[16] From these subscores, physical (PCS) and mental (MCS) health component scores may also be calculated.[17,18] In the present study, the SF-36v2 was administered annually to caretakers during clinic visits, yielding 735 baseline visit responses and 227 responses at 5 years. Most SF-36v2 responses were provided by the mother or other female caretaker. SF-36v2 component scores for PCS and MCS were calculated as described previously.[19]

Statistical analysis

Descriptive statistical analysis was used to characterize child and caretaker ages, race, and ethnicity. Clinical severity of Rett syndrome was assessed in each participant using the Clinical Severity Scale (CSS).[3] Puberty and menarche were assessed at each study visit. Body mass index (BMI) *z* scores were obtained using the Centers for Disease Control and Prevention child growth standard charts.[20] *MECP2* mutations were categorized based on prior interactions with phenotypic measures[3,21]: (1) mild mutations included R133C, R294X, R306C, and 3′ truncations; (2) moderate mutations included T158M and other mutations; and (3) severe mutations included R106W, R168X, R255X, R270X, and large deletions.

Analysis of covariance was used to assess the association of demographic and clinical characteristics with PCS and MCS, respectively. A general linear model was used to obtain the final model including significant factors. A backward selection was used from the model including the factors with analysis of covariance P value <0.01. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc), and two-sided P value <0.05 was considered to represent a statistical significance. No adjustment was made for P values because of multiple comparisons given that each factor was examined according to the authors' hypothesis.

Results

Description of population

After excluding male participants, those living in group homes or institutions, and females who did not meet consensus criteria for classic Rett syndrome, 727 participants and their caretakers were analyzed (Table 1). A total of 220 (30%) participants had 5 years of follow-up. Ages and demographic information are described in Table 1. The average mother's age was 28.9 years at child's delivery and 38.3 years when entering the study. The average child's age at study entry was 9.2 years. Demographics for the participants indicate that most of the participants were white (82.4%), 4.3% were black, and 13.3% were Hispanic–Latino. 46 (6.3%) participants were adopted. Most participants (699 or 96%)

TABLE 1.
Rett Syndrome Caretaker (Baseline) Demographics

	Mean (S.D.)	Median (interquartile range [IQR]s)
Mother's age at delivery	28.9 (5.7)	29 (25-33)
Mother age (at baseline visit)	38.3 (9.0)	37 (32-44)
Father age (at baseline visit)	40.5 (9.5)	39 (34-46)
Child age (at baseline visit)	9.2 (8.3)	6 (3-13)
Ethnicity	n = 727	%
White	599	82.4
Black	31	4.3
Asian	28	3.9
American Indian/Alaskan Native	4	0.6
Native Hawaiian/Pacific Islander	2	0.3
Other	14	1.9
More than one race	49	6.6

had an *MECP2* mutation. The racial and ethnic characteristics were similar at baseline and the 5-year time points.

Quality of life for caretakers

PCS and MCS were analyzed both at baseline and 5-year visit. At both time points, caretaker PCS was higher than MCS. At the baseline visit, mean PCS was 52.8 (9.7), and mean MCS was 44.5 (12.1). For the group of participants with 5-year follow-up, baseline scores were slightly lower for PCS of 51.0 (10.2) and similar for MCS of 44.8 (11.6) and revealed no significant difference between baseline and 5-year PCS ($P = 0.623$) or MCS ($P = 0.132$).

Predictor variables

Table 2 shows the relationships between specific variables and the caretaker PCS and MCS scores. Increasing child age was associated with decreased caretaker PCS and increased caretaker MCS. Increasing maternal caretaker age was associated with decreased caretaker PCS and increased caretaker MCS (data not described). No clear association was seen between age of regression and caretaker quality of life. However, an older age at diagnosis was associated with poorer caretaker PCS ($P < 0.001$) and improved caretaker MCS ($P = 0.05$), and a greater time period beyond the age of regression was associated with poorer caretaker PCS ($P < 0.001$) and improved caretaker MCS ($P < 0.001$).

The severity of disease, measured by the CSS, was associated with a significant change in PCS and MCS. More severe disease was associated with poorer PCS ($P = 0.006$) but improved MCS ($P = 0.003$). Mutation type was not associated with a difference in PCS or MCS. Caretakers of premenarchal females had higher PCS ($P < 0.001$) but lower MCS ($P < 0.001$). BMI did not have a significant impact on PCS, but higher BMI was associated with poorer MCS ($P = 0.002$).

Table 3 shows the relationship between patient functional characteristics and caretaker quality of life. Language ability was not associated with a difference in quality of life. Ambulation was not associated with a significant effect on PCS; and its association ($P = 0.003$) with caretaker MCS did not demonstrate a dose-response relationship for more severe presentations. Ability to sit was not associated with significant variation in quality of life. However, seizure activity was associated with a significant change in PCS ($P < 0.001$), but again not in a dose-response relationship for more severe seizure activity. Breathing, grimacing, and fractures were not associated with significant differences in PCS or MCS. Feeding problems adversely impacted both PCS ($P = 0.007$) and MCS ($P = 0.018$). Gastroesophageal reflux was associated with poorer caretaker MCS ($P = 0.006$), and constipation was associated with poorer caretaker PCS ($P = 0.04$).

In Table 4, nine CHQ questions regarding aspects of parental quality of life grouped in three areas, i.e., increased personal emotional worry, a lack of time for personal needs, and poor family dynamics, were correlated with poorer MCS. However, only three of these nine items were associated with significantly poorer PCS, and only one item, "During the past 4 weeks, were you limited in the amount of time you had for your own needs because of your child's physical health?" described a linear response with a lower PCS for greater limitation ($P < 0.001$).

No significant differences were demonstrated between adoptive or nonadoptive caregivers for PCS ($P = 0.87$) or MCS ($P = 0.49$), and no significant differences were detected between caregivers of white versus nonwhite children for PCS ($P = 0.27$) or for MCS ($P = 0.16$).

TABLE 2.
Patient Characteristics and Caretaker Quality of Life

Visit Variables	Subgroups	n	%	PCS*		MCS†	
				Mean (S.D.); Parameter Estimate (Standard Error [SE])	*P* Value	Mean (S.D.); Parameter Estimate (SE)	*P* Value
Years beyond regression	0-3 years	327	45.0	55.3 (8.2)	<0.001‡	42.4 (12.7)	<0.001‡
	3-6 years	117	16.1	51.7 (9.4)		45.3 (11.5)	
	6-9 years	76	10.5	52.5 (11.1)		45.2 (11.3)	
	9-12 years	44	6.1	48.7 (10.9)		45.9 (14.4)	
	>12 years	163	22.4	50.1 (10.3)		47.3 (10.3)	
Clinical severity score	21 and below	352	48.6	53.8 (9.1)	0.006‡	43.1 (12.9)	0.003‡
	22 and above	372	51.4	51.9 (10.1)		45.7 (11.2)	
Pubertal status (baseline visit)	Premenarchal	548	75.4	53.9 (9.3)	<0.001‡	43.6 (12.3)	<0.001‡
	Postmenarchal	179	24.6	49.6 (10.2)		47.3 (11.1)	

* PCS is SF-36v2 Physical Component Score.
† MCS is SF-36v2 Mental Component Score.
‡ *P* value significant at 0.05 level.

TABLE 3.
Patient Functional Characteristics and Caretaker Quality of Life

Visit Variables	Subgroups	n	%	PCS*		MCS†	
				Mean (S.D.); Parameter Estimate (Standard Error [SE])	*P* Value	Mean (S.D.); Parameter Estimate (SE)	*P* Value
Language	Preserved, contextual	2	0.3	48.3 (6.0)	0.18	47.2 (16.0)	0.25
	Short phrases only	8	1.1	53.1 (14.0)		41.0 (15.7)	
	Single words	87	12.0	51.7 (11.7)		42.9 (13.7)	
	Vocalization, babbling	509	70.0	53.4 (9.1)		44.3 (12.0)	
	Screaming, no utterances	121	16.6	51.4 (10.1)		46.4 (10.9)	
Ambulation	Acquired <18 mo	183	25.2	53.8 (8.3)	0.12	44.4 (12.6)	0.003‡
	Walks alone 18-30 mo	133	18.3	52.7 (9.7)		41.3 (13.1)	
	Walks alone >30 mo	29	4.0	52.6 (8.2)		48.8 (11.4)	
	Walks with help >50 mo	86	11.8	53.2 (9.6)		45.4 (11.6)	
	Acquired and then lost	49	6.7	49.2 (12.6)		48.1 (10.3)	
	Never acquired	247	34.0	52.8 (10.0)		44.7 (11.5)	
Gross motor function	Sits alone acquired 8 mo	401	55.2	53.6 (9.1)	0.11	44.3 (12.1)	0.06
	Sit with delayed acquisition >8 mo and ≤30 mo	193	26.5	52.4 (10.4)		44.2 (12.8)	
	Sit with delayed acquisition >30 mo	11	1.5	48.4 (9.8)		43.5 (10.6)	
	Acquired and then lost	76	10.5	51.8 (9.9)		47.8 (9.2)	
	Never acquired	46	6.3	51.1 (10.5)		41.4 (12.8)	
Seizures	None, without or with medications	516	71.0	53.7 (9.1)	<0.001‡	44.1 (12.3)	0.4
	Monthly	87	12.0	50.6 (9.4)		44.4 (13.3)	
	Weekly	74	10.2	49.4 (13.1)		45.9 (10.9)	
	Daily	50	6.9	52.4 (8.7)		46.5 (10.0)	
Breathing abnormalities	None	199	27.4	53.5 (9.8)	0.62	45.2 (12.0)	0.62
	Minimal hyperventilation and/or apnea (<10% of time)	209	28.7	52.5 (10.0)		43.6 (13.3)	
	Intermittent hyperventilation and/or apnea (50% of time)	239	32.9	52.9 (9.6)		44.6 (10.9)	
	Constant hyperventilation and/or apnea	80	11.0	52.1 (8.5)		44.3 (12.8)	
Prominent grimacing	No	640	88.0	52.9 (9.8)	0.53	44.6 (12.2)	0.52
	Yes	87	12.0	52.2 (9.0)		43.7 (12.0)	
Fractures	No fractures	665	91.5	53.0 (9.5)	0.11	44.2 (12.1)	0.06‡
	Any# fractures	62	8.5	50.9 (11.7)		47.3 (12.2)	
Feeding problems	None	216	29.7	54.4 (8.5)	0.007‡	45.6 (11.2)	0.018‡
	Occasional choking/gagging	180	24.8	52.8 (9.7)		45.0 (12.6)	
	>30 min to feed	201	27.6	52.7 (10.0)		44.7 (12.2)	
	Oral and gastrostomy feeding	84	11.6	50.5 (9.8)		42.8 (12.4)	
	Gastrostomy only	46	6.3	50.2 (11.8)		39.4 (12.8)	
Gastroesophageal reflux	No	395	54.3	53.3 (9.3)	0.19	45.6 (11.8)	0.006‡
	Yes	332	45.7	52.3 (10.1)		43.1 (12.3)	
Constipation	No	155	21.3	54.3 (9.3)	0.04‡	44.3 (11.7)	0.82
	Yes	572	78.7	52.5 (9.7)		44.5 (12.2)	

* PCS is SF-36v2 Physical Component Score.
† MCS is SF-36v2 Mental Component Score.
‡ *P* value significant at 0.05 level.

Multivariate analysis

Multivariate predictors of quality of life are described in Table 5. Only significant values are displayed. A longer interval beyond regression was associated with poorer PCS. Caretakers who felt limited in the amount of time for their own needs also had poorer PCS, as did caretakers who sensed tension or conflict in the home.

For caretaker MCS, increased child's age was associated with an improved score. Feeding problems were associated with poorer MCS. Finally, CHQ items associated with personal worry, lack of time for personal needs, and poor family dynamics described a relationship between increasing severity and poorer MCS.

Discussion

In this study of prospectively gathered data related to caretakers of individuals with Rett syndrome, we examined the relationship of demographic, clinical, and psychological variables on caretaker quality of life. Remarkably, the composites scores described no change between baseline and the 5-year assessment. Overall, the differences between PCS and MCS are similar for parent caretakers of children in other chronic diseases. For Rett syndrome, clinical severity, as measured by the CSS, associated with poorer PCS but with improved MCS.

Questions in the participant quality of life (CHQ) specifically addressing the family's emotional distress, personal

TABLE 4.
Patient Characteristics and Caretaker Quality of Life

Baseline Visit Variables	Subgroups	n	%	PCS*		MCS†	
				Mean (S.D.)	*P* Value	Mean (S.D.)	*P* Value
Emotional worry caused by child's physical health	None at all	62	8.8	52.9 (9.1)	0.86	49.9 (9.7)	<0.001‡
	A little bit	136	19.3	53.3 (8.4)		47.9 (9.9)	
	Some	128	18.1	52.9 (8.1)		47.5 (9.9)	
	Quite a bit	164	23.2	52.3 (10.2)		43.6 (11.7)	
	A lot	216	30.6	53.2 (10.7)		39.1 (13.5)	
Emotional worry caused by child's emotional well-being	None at all	104	14.8	52.0 (10.1)	0.6	51.3 (8.0)	<0.001‡
	A little bit	144	20.4	53.6 (8.3)		48.4 (9.6)	
	Some	144	20.4	52.8 (7.6)		46.6 (9.9)	
	Quite a bit	137	19.4	52.5 (10.6)		41.4 (11.8)	
	A lot	176	25.0	53.6 (10.5)		37.3 (13.7)	
Emotional worry caused by child's learning abilities	None at all	110	15.6	51.2 (9.4)	0.033‡	50.6 (8.1)	<0.001‡
	A little bit	103	14.6	53.4 (8.2)		47.0 (9.5)	
	Some	134	19.0	52.1 (8.4)		45.5 (10.7)	
	Quite a bit	134	19.0	54.9 (9.8)		43.4 (12.1)	
	A lot	225	31.9	52.9 (10.5)		39.8 (13.7)	
Limitations for your personal needs caused by child's physical health	Yes, limited a lot	204	28.8	50.8 (11.3)	<0.001‡	40.3 (13.4)	<0.001‡
	Yes, limited some	212	29.9	53.2 (9.1)		43.6 (11.8)	
	Yes, limited a little	128	18.1	53.6 (9.0)		46.5 (10.8)	
	No, not limited at all	164	23.2	54.7 (7.7)		48.7 (9.8)	
Limitations for your personal needs caused by child's emotional well-being	Yes, limited a lot	158	22.3	51.5 (11.4)	0.096	37.7 (13.5)	<0.001
	Yes, limited some	182	25.7	53.9 (8.5)		42.2 (11.7)	
	Yes, limited a little	148	20.9	52.5 (9.1)		46.4 (11.0)	
	No, not limited at all	219	31.0	53.4 (9.3)		49.5 (9.2)	
Limitations for your personal needs caused by child's learning abilities	Yes, limited a lot	176	24.9	51.8 (10.9)	0.36	38.6 (13.5)	<0.001‡
	Yes, limited some	187	26.4	53.4 (9.3)		44.0 (11.9)	
	Yes, limited a little	132	18.7	53.4 (8.8)		45.0 (11.2)	
	No, not limited at all	212	30.0	53.0 (9.2)		49.0 (9.3)	
Frequency that child's health or behavior has caused tension at home	Very often	67	9.5	53.2 (9.8)	0.037‡	34.9 (13.2)	<0.001‡
	Fairly often	61	8.6	51.9 (11.0)		38.4 (13.3)	
	Sometimes	219	30.9	53.3 (9.2)		42.3 (11.7)	
	Almost never	168	23.7	54.4 (7.7)		46.6 (10.7)	
	Never	193	27.3	51.4 (10.7)		49.9 (9.4)	
Frequency that child's behavior has been a source of disagreements at home	Very often	38	5.4	54.3 (9.0)	0.36	32.6 (12.8)	<0.001‡
	Fairly often	40	5.6	52.4 (10.6)		37.9 (13.3)	
	Sometimes	170	24.0	53.1 (9.6)		41.3 (12.2)	
	Almost never	205	29.0	53.7 (8.7)		44.6 (11.2)	
	Never	255	36.0	52.0 (10.2)		49.0 (10.1)	
Rating of family's ability to get along with one another	Poor	8	1.1	52.4 (8.2)	0.87	28.1 (9.4)	<0.001‡
	Fair	46	6.5	52.9 (8.8)		38.5 (13.2)	
	Good	161	22.7	52.8 (9.8)		40.7 (13.2)	
	Very good	309	43.6	52.6 (10.0)		44.9 (11.1)	
	Excellent	184	26.0	53.5 (8.9)		48.8 (10.5)	

* PCS is SF-36v2 Physical Component Score.
† MCS is SF-36v2 Mental Component Score.
‡ *P* Value significant at 0.05 level.

needs, and family dynamics were strongly associated with MCS, and a multivariate model described that feeding problems were associated with poorer caretaker MCS.

Comparing quality of life to other chronic diseases

In our study, caretaker MCS was consistently lower than PCS, a trend that has been displayed for caretakers of other chronic diseases. In Japanese children (n = 149) with pervasive developmental disorders, mothers had average PCS of 50.3 (6.9) and MCS of 42.9 (11.9).[22] For Serbian children (n = 49) with Rett syndrome, mothers had average PCS of 54.2 (28.4) and MCS of 46.1 (29.6).[9] In a study of children (n = 250) with Down syndrome, mothers had average PCS of 50.2 (9.6) and MCS of 45.2 (10.6). This pattern of lower relative MCS holds for this study's population as well. The PCS and MCS scores of 35- to 44-year-old women from the US general population are 51.6 (8.6) and 47.8 (10.4), respectively.[23] For caretakers of those with Rett syndrome, this demonstrates similarity of PCS to the general population but lower MCS scores at 44.6 (12.1). Interestingly, caretakers in Rett syndrome seem to be more affected mentally than physically by their significant responsibilities. In comparison, cerebral palsy, a disease with more distinctly physical disability, has been demonstrated to affect both caregiver psychological and physical quality of life[24,25]; however, when the SF-36v2 instrument has been used, disease severity of CP did not adversely affect physical functioning quality of life but affected all other aspects of quality of life.[26]

TABLE 5.
Multivariate Regression of Predictors of Caretaker Quality of Life

	PCS*		MCS†	
	PE (SE)	*P* Value	PE (SE)	*P* Value
Child's age			0.20 (0.05)	<0.001‡
Years beyond regression		<0.001‡		
0-3	Ref			
3-6	−3.36 (1.00)	<0.001		
6-9	−2.14 (1.19)	0.072		
9-12	−5.95 (1.50)	<0.001		
>12	−4.81 (0.91)	<0.001		
Feeding problem				<0.001‡
None			Ref	
Occasional choking/gagging			0.25 (1.05)	0.81
>30 min to feed			−0.04 (1.01)	0.97
Oral and gastrostomy feeding			−2.12 (1.35)	0.12
Gastrostomy only			−7.42 (1.68)	<0.001
Emotional worry caused by child's emotional well-being				<0.001
None at all			Ref	
A little bit			−1.09 (1.33)	0.41
Some			−1.48 (1.36)	0.28
Quite a bit			−6.34 (1.38)	<0.001
A lot			−8.59 (1.42)	<0.001
Limitations for your personal needs caused by child's physical health		<0.001‡		
No, not limited at all	Ref			
Yes, limited a little	−1.40 (1.10)	0.201		
Yes, limited some	−1.92 (0.99)	0.052		
Yes, limited a lot	−4.19 (1.03)	<0.001		
Limitations for your personal needs caused by child's learning abilities				0.002‡
No, not limited at all			Ref	
Yes, limited a little			−2.49 (1.15)	0.031
Yes, limited some			−0.25 (1.10)	0.82
Yes, limited a lot			−3.73 (1.19)	0.002
Frequency that child's health or behavior has caused tension at home		0.026‡		<0.001‡
Never	Ref		Ref	
Almost never	2.90 (0.99)	0.003	−2.52 (1.11)	0.023
Sometimes	2.25 (0.94)	0.017	−3.65 (1.12)	0.001
Fairly often	1.53 (1.40)	0.275	−6.11 (1.63)	<0.001
Very often	3.22 (1.38)	0.019	−6.47 (1.65)	<0.001
Rating of family's ability to get along with one another				<0.001‡
Excellent			Ref	
Very good			−2.95 (0.98)	0.003
Good			−5.95 (1.18)	<0.001
Fair			−6.97 (1.77)	<0.001
Poor			−16.3 (3.72)	<0.001

Abbreviations:
PE = regression parameter estimate
SE = standard error
* PCS is SF-36v2 Physical Component Score.
† MCS is SF-36v2 Mental Component Score.
‡ *P* value significant at 0.05 level.

PCS and MCS in caretakers

We also found that markers of more severe disease do not have uniformly deleterious effects on caretaker quality of life, and in fact, some variables that indicate worse MCS scores can lead to improvement in PCS scores. This effect has been demonstrated previously for participants with Rett syndrome: more severe clinical status and motor impairment were associated with improved psychosocial quality of life, although these more severe phenotypes were associated with lower physical quality of life.[7] This finding could possibly be explained by the fact that greater physical impairment reduces the likelihood of engaging in problematic or risky behaviors.[7] We also found that specific mutations did not correlate with caretaker quality of life, a result that has been described for individuals with Rett syndrome themselves. Specific mutations are understood to confer differing degrees of disease severity, with particular mutations increasing the likelihood that a given individual will retain hand use, speech, or ambulation,[3] but at the individual level, the variation is large enough to confound this type of analysis. Ambulation was significantly correlated with MCS, but not in a linear fashion. Ambulation is a trait that we hypothesized might contribute to increased behavioral difficulties for a caregiver.

Previous research on caretaker quality of life in Rett syndrome described that education beyond high school was associated with poorer physical health and that a mother

working outside the home was associated with improved mental health.[8] Better physical health was associated with adequate time resources for family needs.[8] Among clinical attributes, only breathing problems were associated with poorer physical health outcomes.[8] Fractures and facial stereotypies were associated with poorer mental health.[8] Our work differs from this previous research in that we did not find a significant effect for breathing problems, fractures, or grimacing. These different findings may be explained by the use of the SF-36v2 instrument in the present study as opposed to the SF-12 instrument by Laurvick et al.[8] These findings could also be explained by the larger number of clinical patient variables that were used in the present study or the use of categorical variables as opposed to dichotomous ones.

Feeding issues appear to be important for caretaker quality of life and are unique in that more severe feeding issues are correlated with both poorer PCS and poorer MCS in univariate analysis. However, in multivariate analysis, feeding issues were only associated with poorer MCS. Feeding issues may represent an important clinical target for physicians, affording an opportunity to improve patient well-being and caretaker quality of life. Gastrointestinal problems are prevalent in Rett syndrome, placing significant burden on both children with Rett syndrome and their caregivers.[27] Existing recommendations have suggested that gastrostomy may provide an improved quality of life for caretakers in Rett syndrome[28] as supported by the prior reports to this effect.[29,30] The relationship between increasing BMI and poorer MCS may suggest that the quality-of-life issues related to feeding are not driven simply by nutritional status.

Value of the CHQ items

Not surprisingly, the CHQ items that address caretaker emotional worry, personal needs, and family dynamics have very strong correlations to caretaker quality of life as measured by MCS. In chronic pediatric illnesses, a parent may be asked to take on new roles in managing a child's health in addition to his or her traditional responsibilities. A variety of factors have been identified which predict parental quality of life in these settings, including personal characteristics, psychological traits, socioeconomic status, child behavior, caregiving demands, family function, and social support.[24,31] In addition to managing the child's burden of disease, some identify the family as the key target for interventions, empowering parents and families to respond more effectively to the responsibilities of caregiving.[24] It should also be demonstrated that caregiving for a chronic illness is a dynamic role for parents, changing over time as both the child and the parent ages and progressing through different stages, from the initial acceptance of the role, through its execution, and ultimately, exit from it.[24]

Limitations

Several weaknesses are demonstrated in our characterization of caretakers. We did not capture the specific relationship of the caretaker to the child, and we did not capture gender on the SF-36v2 form. Thus we only use the term caretaker, and we can only estimate the relationship and gender of the individual filling out the SF-36v2 form; however, approximately 95% of the primary caregivers that completed the form were biological mothers. We do not have marital, financial, educational, or other family data about the caretaker; nonetheless, these effects have been well characterized in previous work.[8] Another issue is the difference in the number of caretaker responses at baseline and at 5 years. In spite of this difference (727 to 220 responses), the responses were remarkably similar. In Tables 4 and 5, PSC results for "emotional worry caused by child's learning abilities" (Table 4) or "frequency that child's health of behavior has caused tension at home" (Tables 4 and 5), although significant, described no clear trend and could be affected by other clinical features not assessed by this instrument.

Conclusion

Caretaker quality of life in Rett syndrome is similar to that for caretakers in other chronic diseases, including other neurodevelopmental disorders. Specifically, for Rett syndrome, several disease features have important associations with caretaker quality of life. In univariate analysis, increased clinical severity is associated with poorer caretaker PCS and improved caretaker MCS, and feeding difficulties are associated with both poorer PCS and MCS. However, in multivariate analysis, feeding difficulty was the only clinical measure described to impact caretaker quality of life. Thus feeding issues may represent an important clinical target for improving both child and caretaker quality of life and may warrant increased attention from both clinicians and researchers.

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