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Assessment of Caregiver Inventory for Rett Syndrome

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Abstract

Rett syndrome (RTT) requires total caregiver attention and leads to potential difficulties throughout life. The Caregiver Burden Inventory, designed for Alzheimer disease, was modified to a RTT Caregiver Inventory Assessment (RTT CIA). Reliability and face, construct, and concurrent validity were assessed in caregivers of individuals with RTT. Chi-square or Fisher's exact test for categorical variables and t-tests or Wilcoxon two-sample tests for continuous variables were utilized. Survey completed by 198 caregivers; 70 caregivers completed follow-up assessment. Exploratory factor analysis revealed good agreement for Physical Burden, Emotional Burden, and Social Burden. Internal reliability was high (Cronbach's alpha: 0.898). RTT CIA represents a reliable and valid measure, providing a needed metric of caregiver burden in this disorder.

Keywords

Rett syndrome; Caregiver Inventory; *MECP2*; factor analysis

Rett syndrome (RTT), first described by Andreas Rett (Rett 1966) in 1966, is a complex monogenic disorder involving significant medical, behavioral, and neurologic issues. RTT is caused by an X-chromosome mutation (Xq28) in the gene, methyl-CpG-binding protein 2 (*MECP2*), occurring almost exclusively in females. Diagnosis is based on consensus clinical criteria established by an international panel, as up to 4% of those with clinical features of RTT lack an identified mutation in *MECP2*. RTT has been described in all ethnic and racial

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populations with approximately equal frequency. The annual incidence is approximately 1 per 10,000 live female births (Laurvick et al. 2006a).

RTT is characterized by arrested development and regression generally between 12 and 30 months of age with partial or complete loss of communication and fine motor skills, stereotypic movements (principally of the hands), and absent or dyspraxic gait. Defining intelligence level is difficult due to inability to complete standard IQ tests. Growth failure, gastrointestinal problems, epilepsy, periodic breathing, scoliosis, and other medical issues are prominent in most (Glaze et al. 2010, Percy et al. 2010, Pintaudi et al. 2010, McCauley et al. 2011, Motil et al. 2012, Tarquinio et al. 2012). Autism may be suspected in the second year of life, but these features are generally absent thereafter. Survival beyond the fifth decade is expected (Kirby et al. 2010). Thus, caregivers must provide total care throughout life, placing significant burden on them.

The impact of long-term caregiving on family caregivers has been examined across a number of disorders including dementia/Alzheimer disease (Lavretsky 2005, Garcia-Alberca et al. 2011), chronic illnesses such as cerebral palsy and cancer (von Essen et al. 2004, Raina et al. 2005, Klassen et al. 2008, Davis et al. 2010), and in psychiatric (Knock et al. 2011) and developmental disorders (Williamson and Perkins 2014). Caregiving for an individual with complex psychiatric, developmental or medical disorders has been shown to have a significant impact on family caregivers including higher perceived caregiver burden (Angold et al. 1998, Bussing et al. 2003, Iosif et al. 2013, Vaughan et al. 2013, Kirby et al. 2015), lower quality of life (Mugno et al. 2007, Kuhlthau et al. 2010, Feeley et al. 2014, Hoefman et al. 2014), poorer physical health (Meltzer and Mindell 2006, Murphy et al. 2007, Feeley et al. 2014) and higher levels of depression and lower level of overall psychological well-being (Abbeduto et al. 2004, Ha et al. 2008, Estes et al. 2009, Yamaki et al. 2009). It has been shown to be correlated as well with physiological markers of stress (Lovell et al. 2012a, Lovell et al. 2012b, Iosif et al. 2013).

While key areas of impact are common to caregivers across disorders (e.g. perceived burden, quality of life, physical health, mental health and economic impact), the type and degree of burden on caregivers varies according to the specific disorder. Caregivers of individuals with Down syndrome have been found to experience less burden from caregiving compared to caregivers of individuals with other developmental disorders including lower levels of stress and better psychological well-being (Abbeduto et al. 2004, Esbensen and Seltzer 2011). Abbeduto et al. (Abbeduto et al. 2004) also found that while caregivers with FXS have lower well-being than caregivers of individuals with Down Syndrome, they have better well-being than caregivers of individuals with ASD. In other studies, caregivers of individuals with ASD have been observed to experience higher levels of caregiver burden, stress, health and psychological impairment than caregivers of individuals with ADHD, or general developmental delay or behavioral impairment (Estes et al. 2009, Cadman et al. 2012, Kirby et al. 2015).

Consideration of whether these differences are due to disorder-specific symptoms, the higher likelihood of certain negative patient characteristics such as problem behaviors being present in the disorder, or caregiver characteristics is complex (Greenberg et al. 1993, Lecavalier et

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al. 2006, Esbensen and Seltzer 2011, Mao 2012, Vaughan et al. 2013, Ruiz-Robledillo et al. 2014, Vogan et al. 2014, Lovell and Wetherell 2015). However, these observations of differences across disorders highlight the importance of considering how the specific manifestations of the disorder may impact caregivers and influence perceptions of caregiver burden. While the broad areas of concern may be in common, assessing the level of burden in particular may require taking into consideration the specific challenges and even perceived positive aspects of caregiving in various disorders. For this reason, the development of disorder-specific measures is important (Chow et al. 2013, Hoefman et al. 2014).

Although the long-term burden of caregiving for Rett families has been recognized amongst clinicians, there has been little specific, systematic research on caregiver burden in RTT. Laurvick et al. 2006b (Laurvick et al. 2006b) reported their findings from the Australian Rett syndrome Registry database, where they assessed mental and physical health of mothers of individuals with RTT using the physical and mental health component scores of the SF-12, aimed to identify factors that were positively related to good mental and physical health amongst mothers of Rett individuals. As expected, the physical and mental health scores for mothers of individuals with Rett were lower than the standard average scores and average scores for a community based sample in Australia. Laurick et al. (Laurvick et al. 2006b) identify three factors that related to higher mental and physical health: child behavior, caregiver demands and family function. This included for mental health: child factors (less reporting of stereotypies and involuntary facial movements, child not having a fracture in the last 2 years), social factors (being in a well-adjusted marriage, mother working full or part-time) and caregiver characteristics (low stress scores). Better scores on physical health were likewise attributable to a number of factors including social factors (mother working full-time or part-time, having some high school education, having private health insurance, adequacy of time resources for basic and family needs) and child factors (child not having breathing problems in the last 2 years, child not having structured home-based therapy). With respect to more systematic assessments of caregiver burden, in the absence of a specific measure of the caregiver concerns for RTT, the problem has been acknowledged only tangentially.

An assessment of caregiver impact specific to RTT is considered to be highly relevant and important among families, physicians, and patient advocates as this is a disabling disorder requiring lifelong care of those affected. As no inventory of the potential impact of RTT is currently available, the Caregiver Inventory for Rett Syndrome was developed. This RTT-specific caregiver burden assessment was originally developed for use as an exploratory efficacy measure in a treatment trial of trofinetide in adolescent and adults with RTT (Jones et al. 2014, Glaze et al. 2015). The intent of using this type of scale in a treatment trial was to assay indirectly the significance of treatment effect on function in the context of activities of daily living by virtue of directly assessing caregiver burden.

Given that our aim was to examine factors that could be impacted in the course of a relatively short period of a treatment trial, we focused on assessment of caregiver burden, which we defined as caregiver's perceived level of burden (Hunt 2003). This construct would also be appropriate for looking at longer-term outcomes in conjunction with other

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types of measures. Caregiver burden encapsulates the caregivers' perceived impact of caregiving on their daily tasks (ability to work, having time for activities), relationship with other family members, health and well-being, feelings about their caregiving and the person for whom care is provided.

For this purpose, criteria considered for an appropriate scale represented the inclusion of items across different dimensions of burden, items that had potential to be responsive to changes seen in the relatively short duration of the trial, and the number of items included to ensure the burden in terms of time and effort to complete the scale was reasonable.

Many surveys of caregiver concerns have focused largely on the elderly and issues of cognitive impairment such as in Alzheimer disease (Zarit et al. 1980, Robinson 1983, Morycz 1985, Schwartz et al. 2012), but these instruments are unidimensional, providing a single score, and do not allow the factoring of items into different aspects or constructs. Other surveys (Niederehe and Fruge 1984, Poulshock and Deimling 1984, Kosberg and Cairl 1986, Deeken et al. 2003, Whalen and Buchholz 2009) have responded to this weakness by creating multidimensional approaches, but have been regarded as problematic due to the overly large number of questions, inadequate subscales, or concerns for interdependence of the individual subscales. More recently, caregiver studies have been conducted on multiple sclerosis (McKenzie et al. 2015) and Down syndrome (Esbensen and Seltzer 2011), both using the Zarit unidimensional scale.

To advance this study in RTT and to avoid a unidimensional scale, a questionnaire designed a quarter century ago by Novak and Guest for Alzheimer disease, the Caregiver Burden Inventory (Novak and Guest 1989) was adapted. This model was selected because it allowed analysis of different dimensions of burden that are not possible with the single burden score, but yet is not overly long so as to be burdensome to complete (Jones et al. 2014). In this paper, we describe the validity and psychometric properties of this adapted scale, the RTT Caregiver Inventory Assessment (RTT CIA), based on data from a validation study conducted as part of the Rett Syndrome Natural History study (NCT00299312).

Methods

Sampling Procedures

One or both parent caregivers of participants in the on-going Rett Syndrome Natural History Study were invited to participate in this study as part of one of their study clinic visits in 2014. Caregivers were asked to repeat the study tasks at a follow-up time point approximately 3 months later via mail to assess test-retest reliability. These caregivers included both those coping with the new diagnosis and others where aging was becoming a more significant factor in order to capture the range of caregiver burden across the study group and spectrum of disease. The sampling procedure involved a subset of individuals participating in the Rett Syndrome Natural History Study which is a collaboration of four RTT clinical centers: University of Alabama at Birmingham, Baylor College of Medicine, Greenwood Genetic Center, and Boston Children's Hospital (Harvard) and four travel clinics. The sampling for this study was conducted at data collection weekends at travel clinics held in Oakland, CA, Chicago, IL, and Miami, FL and at the Rett Syndrome Clinic at

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the University of Alabama at Birmingham, Birmingham, AL. No randomization procedures were employed. This group represented 20.5% of all individuals enrolled in the Natural History Study and consisted of a cross-section of the total group with virtually identical characteristics in terms of age range, clinical severity, mutation type, growth parameters, and racial/ethnic background.

Human Studies Approval

Approval for the RTT CIA validation as an Exempt protocol was obtained from the institutional review board at UAB as the lead site.

Data Collection

Parent caregivers were asked to complete a brief demographic information section about themselves and their child with RTT at the initial visit. One or both caregivers for a child with RTT provided answers, one for each parent, to this instrument. In instances where both parents did provide answers, no effort was made to link the answers in order to allow for and provide independent responses and to maintain anonymity. The caregiver's age, race and ethnicity, and their child's age in years and months as well as the age at diagnosis were collected. While this could be used in many instances to link responses, we did not do this as per our commitment to the respondents of an anonymous survey. Additionally, limited clinical information regarding the *MECP2* genetic mutation information, clinical severity categories (Clinical Severity Scale-CSS and Motor Behavioral Assessment-MBA), and the current Body Mass Index about those with RTT were provided to the caregiver by the clinicians. Finally, caregivers completed the questionnaire regarding caregiver burden at this initial visit and at the following 3-month interval, returning this anonymously by an on-site drop box at the initial visit or by mail at the follow-up interval. By providing caregivers with data forms that were linked by a unique numbering and lettering system (ID number+ A = Baseline; ID number+ B = Follow-up), the two datasets were able to be matched while respondents remained anonymous. While both time points were linked, the purpose here is primarily to examine the properties of the survey at the initial visit. Data from assessments collected as part of the Rett Syndrome Natural History Study including demographic and RTT characteristics (e.g. age, *MECP2* mutation type), symptom severity and health status (e.g. CSS and MBA), after removing linked identifiers, were also collected. The assessments for the Rett Syndrome Natural History Study are described in more detail in (Neul et al. 2008). In brief, the demographic and clinical history data are collected from the caregiver. The specific mutation type was collected and categorized as no mutation; R133C, R294X, R306C, and 3' truncation (group 1); R168X, R255X, R270X, large deletion (group 2); R106W, T158M (group 3); and other mutations (group 4 includes other point mutations, insertion, or insertion/deletion).

Clinical severity, as noted above, was assessed by study physicians using the CSS and MBA. The CSS measures clinical severity of key diagnostic and developmental features for RTT based on 13 individual, ordinal categories measuring clinical features common in RTT. Scores for all items were summed to create a total score (range 1–58). The MBA components include a behavior/social assessment (range 0–64), orofacial/respiratory assessment (range 0–28), and motor assessment/physical signs (range 0–56). An overall

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score is obtained by summing each of these 3 components (range 0–148). For both measures, higher scores indicate more severe clinical status.

RTT Caregiver Inventory Assessment (RTT CIA)

The original inventory (Novak and Guest 1989) contains 24 elements some of which are not relevant to RTT due to its intended use for older adult caregiving. These were modified to fit the profiles of individuals with RTT, and two positively worded questions were added which were originally scored separately as an “Optimism Index”. The resultant modification contains 26 questions to address issues specific to caring for individuals with RTT derived from the same areas as the original form, namely, Time dependency, Developmental burden, Physical burden, Social burden, and Emotional burden (Jones et al. 2014). Items for the modified version were identified and reviewed for face validity by clinical experts, family members, and advocacy stakeholders. We aimed to evaluate various types of validity and reliability of the modified Caregiver Burden Inventory, the RTT Caregiver Inventory Assessment (RTT CIA), in caregivers responsible for an individual with RTT. In contrast with questions 1–24, questions 25 and 26 were positively worded and as such were reverse scored when calculating the total burden score. The caregivers were informed of the personal nature of the questions and asked to provide answers focusing, in particular, on the prior two weeks and to relate the responses to the whole period, not concentrating on a specific moment in time. The answers to each question were provided by a five point Likert scale: 1) I never feel this way; 2) I rarely feel this way; 3) I sometimes feel this way; 4) I quite frequently feel this way; and 5) I nearly always feel this way. This yields a minimum score of 26 and a maximum score of 130. In addition to the total score of items 1–26, the RTT CIA total score for items 1–24 was calculated to align more closely with the calculations in the original paper of Novak and Guest (Novak and Guest 1989). The questionnaire developed by Novak and Guest (Novak and Guest 1989) was modeled to assess factors related to five domains, namely, Time dependency, Developmental burden, Physical burden, Social burden, and Emotional burden. In the current survey, the discrimination of burden cut across four dimensions. For the RTT CIA modification (see Supplemental File), the items developed were confined to four domains, Physical Burden (questions 9–14), Emotional Burden (questions 7, 8, and 21– 26), Social Burden (questions 15–19), and Time Dependence (questions 1–6 and 20). The rationale for dropping the “Developmental Burden” factor is that the number of items related to this were too few to analyze. This difference from the Novak and Guest questionnaire is felt to represent the decidedly different populations under study, those with RTT in the present study versus those with Alzheimer disease in the Novak and Guest study. The sociological issues related to spousal caregivers versus parental caregivers should not be underestimated. In addition, the age and relationship of the caregivers between the two studies are quite different. In the present study, the caregivers were generally parents of affected individuals whereas in the Novak and Guest study, the caregivers were younger than the participants and were spouses, siblings, or children of affected individuals or unrelated third parties.

Data Analysis

For collection and analysis purposes, the data were de-identified. Differences between the caregivers who completed both time points and those only completing the initial time point

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were compared using chi-square or Fisher's exact test for categorical variables and t-tests or Wilcoxon two-sample tests for continuous variables. The association of the RTT CIA with demographic characteristics, age of diagnosis, symptom severity, and health status were conducted using Pearson correlations. A paired t-test was used to compare change in the RTT CIA between the two time points. Psychometric properties for the RTT CIA were assessed including the preliminary factor structure, reliability (e.g. internal consistency, test-retest) and validity (e.g. content, criterion, concurrent, and predictive). An exploratory factor analysis (EFA) was performed to investigate the factor structure of the RTT CIA (modified CBI) in caregivers of females with RTT. The EFA used the principal axis method with squared multiple correlation as the prior and orthogonal variable rotation for the 26 variables. The scree plot and differences in variance explained were used to determine the number of factors (Cattell 1966). Those missing a response to an item in the RTT CIA were not used in the EFA. Analyses were conducted using SAS 9.4 (Cary, NC).

RESULTS

Participants

198 caregivers participated in the initial survey. Of those caregivers, 70 (35%) completed a follow-up visit. Parent demographics (Table 1) and child clinical characteristics (Table 2) are summarized for all caregivers and their children, for those who completed an initial and follow-up visit (responder), and for those who completed only an initial visit (non-responder). The majority of parents responding to the survey were female (61.6%), non-Hispanic (91.0%), white (88.6%), an average (standard deviation [SD]) age of 45 (9.5) and in very good to excellent health (70.4%). The racial/ethnic distribution of this study differs from that in the US population. A concerted effort has been made to enroll individuals according to the US demographic distribution, but, as in other research studies, recruitment is often difficult from the non-white and Hispanic groups. At follow-up, the parents were all white and slightly older and the children were slightly older and diagnosed at older ages (Table 1 and 2). While these differences are important, the primary interest and data analysis of this study were in the data collected at the first time point.

The average (SD) caregiver burden for all respondents was 61.9 (14.6), less than 50% of the maximum score. The level of burden was similar between responders at follow-up and non-responders (61.2 vs. 62.3, respectively, p=0.63). For the responders, a 1 point increase in the RTT CIA (p=0.19) between the initial and three month follow-up questionnaire was noted.

Correlations

The association of the parent's demographics with the RTT CIA total score and RTT CIA total for items 1–24 showed weak but significant correlations to their general health and health compared to a year ago (Table 3). No other factors were significantly associated with the RTT CIA total score.

Validity

To assess various types of validity, but most importantly construct and face validity, we examined the relationship of the RTT CIA score with characteristics of parents and their

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child (Table 4). The relationship between caregiver burden and the parent's general health showed that with decreased parent health an increase in reported caregiver burden was noted. Similarly, a higher caregiver burden was noted in those parents reporting worse health than a year ago compared to those who were about the same or better. The child mutation types of *Mutation group 4* and *no mutation* were associated with higher caregiver burden. No significant difference was found in the change in caregiver burden for these respondents (p=0.187).

Reliability

Internal consistency was high for the RTT CIA (Cronbach's alpha: 0.910). When looking at the correlation of each item compared with the total, only questions 2 (*completely dependent on me*), 25 *(…raising my daughter also brings me great satisfaction)*, and 26 (*had experiences recently that have given me hope*) have low correlations with the total. Removing each of these items does not offer much improvement in the consistency (Supplemental Table 1). The test-retest correlations were also high between the two time points (r= 0.906, p<0.0001) for the 70 participants who completed the RTT CIA at 3 months.

Factor Analysis

The exploratory factor analysis was conducted using the 177 (89.4%) participants who completed every item in the RTT CIA at the first time point. For those participants who did not have a complete RTT CIA, the majority (n=18 [85.7%]) were missing just one item. The scree plot showed a four factor model should be retained in the model given their eigenvalues were greater than 1 for factors 1–3 and the last was 0.89. These factors explained 88.9% of the total variance (Table 5). Additional details on the EFA are included in the supplementary material. The first factor (eigenvalue=8.3, variance explained = 59.9%) summarizes physical caregiver burden, loaded on questions 9–14 and each of the loadings were greater than 0.5. The second factor (eigenvalue=2.1, variance explained= 15.1%), emotional burden, also had loadings greater than 0.5 for questions 7, 8, 21–26. Social burden was summarized in the third factor (eigenvalue=1.1, variance explained= 7.9%) with questions 15–19 with loadings greater than 0.5 except for question 19 (loading=0.475). Finally, the fourth factor (eigenvalue=0.84, variance explained= 6.1%) loaded on questions 1–6 and 20 and summarized the time dependence of caregiver burden. The first two factors explained 75.0% of the total variance representing physical and emotional caregiver burden.

DISCUSSION

The CIA RTT is an instrument which appears to be adequate for the assessment of burden in caregivers of those with RTT. This study provides evidence to support the reliability and validity of the Caregiver Inventory Assessment for RTT in this population which spans a wide range of disease characteristics. Additional evaluations should be conducted to substantiate these results. In the present study, a stronger association was noted between the CIA and parents' health than with factors related to the individuals with RTT. This is regarded as an important point indicating that the caregiver's own health impacts perceived

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burden. Analysis of the scale independent of this factor results in assessment of only part of the overall picture.

In multiple sclerosis patients using the Zarit caregiver burden tool (Zarit et al. 1980), McKenzie et al. (McKenzie et al. 2015) reported a higher physical burden reported by the male caregivers and more psychological issues by females. Caregivers with more stress (mood disturbances, stress, anxiety, sleep disturbance, and headache) reported higher levels of burden. Also using the Zarit, mothers of individuals with Down syndrome (DS) reported greater levels of burden at younger maternal ages and with fewer social supports. However, individuals with DS are generally in better overall health than individuals with multiple sclerosis and much less likely to require the same level of care as those with RTT (Esbensen and Seltzer 2011).

The Novak and Guest model was selected because it allowed an analysis of the dimensions of burden that are not possible with the single burden score provided by the Zarit used in the two studies described above. When subjected to factor analysis, the discrimination of burden cut across four dimensions, not five, as in the original scale designed and implemented by Novak and Guest (Novak and Guest 1989). This likely represents the decidedly different populations under study, those with RTT in the present study versus those with Alzheimer disease in the original study. The sociological issues related to spousal caregivers versus parental caregivers should not be underestimated. In addition, the age and relationship of the caregivers between the two studies are quite different. In the present study, the caregivers were generally parents of the affected individuals whereas in the Novak and Guest study, the caregivers were younger than the participants being spouses, siblings, or children of the affected individual or unrelated third parties.

Potential deficiencies in this study relate to the ethnic and racial make-up of the study group, the cross-sectional nature of the study, and the significantly smaller group of caregivers who provided follow-up assessments. The study population was dominated by individuals of Caucasian descent and the group providing follow-up assessments was entirely of Caucasian descent. The study population of the RTT Natural History Study (NHS) is virtually identical with the overall make-up of the group in this study as we have complete data on clinical severity, mutation, and growth parameters. This is a recognized shortcoming of the RTT NHS, but is not unique to this disorder in terms of recruitment and enrollment of all ethnic and racial groups. As shown in Table 1, the demographics of the population in this study represents a shortcoming. The lack of association between RTT CIA scores and child's clinical severity represents a relative weakness. It also highlights the challenges of initial validations of instruments as related measures are not available for determining concurrent validity.

This study as reported herein, although demonstrating very good reliability and validity of the measure, was solely cross-sectional. The validity is supported by concurrent, predictive, and face validity as compared to other surveys in other areas for caregivers of long term chronic conditions (i.e. MS). Predictive validity will likely be established by examining the declines in health of the caregivers and subsequent declines in the RTT-CIA. To date, the group providing follow-up assessment after 3 months showed little change. It is very likely

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that a multi-year study would be warranted to assess possible changes in burden over a much longer interval and to associate those changes in burden with changes in child and parental health status. Regarding the group providing follow-up assessments, while the response rate was low, at 35% this rate is not dissimilar from other surveys of this type. Further, the denominator consists of multiple caregivers within the same household and on follow-up it is possible that only one caregiver thought it was necessary to respond. Despite showing slight overall worsening, perhaps reflecting the greater sensitivity of this group to respond, the differences noted were not impressive.

Conclusion

The RTT Caregiver Inventory appears to represent a reliable and valid measure of the impact on the caregiver for providing daily care for an individual with a severe neurodevelopmental disorder manifesting as lifelong dependence on another for all essential needs of daily living. Exploratory factor analysis determined that four factors: physical, emotional, social, and time dependence accounted for 89% of total variance. The first two factors, physical and emotional represented 75% of the total variance. Despite being cross-sectional, this inventory appears to represents a useful tool for assessing caregiver burden in individuals with RTT.

This instrument was designed for individuals with RTT. As such, it might not be useful for all children with special needs. However, items could be modified to be more appropriate generally and the instrument studied across a broader group of special needs children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Parent Demographics

	All (n=198)	Responder (n=70)	Non- Responder (n=128)	p-value
Parent Gender, n (%)				
Female	122 (61.6)	45 (64.2)	77 (60.2)	0.568^
Male	76 (38.4)	25 (32.9)	51 (39.8)	
Parent Ethnicity, n (%)				
Non-Hispanic	171 (91.0)	61 (92.4)	110 (90.2)	0.606^
Hispanic	17 (9.0)	5 (7.6)	12 (9.8)	
Parent Race, n (%)				
White	171 (88.6)	69 (100)	102 (82.3)	
Asian	10 (5.2)	0 (0.0)	10 (8.1)	
Black	4 (2.1)	0 (0.0)	4 (3.2)	<0.0001*
American Indian	1 (0.5)	0 (0.0)	1 (0.8)	
Mixed	2 (1.0)	0 (0.0)	2 (1.6)	
Other	5 (2.6)	0 (0.0)	5 (4.0)	
Parent Age, mean (SD)	45 (9.5)	47 (9.3)	44 (9.5)	0.0209¥
Parent General Health, n (%)				
Excellent	53 (27.0)	22 (31.9)	31 (24.4)	
Very Good	85 (43.4)	27 (39.1)	58 (45.7)	0.0005*
Good	44 (22.5)	15 (21.7)	29 (22.8)	
Fair	11 (5.6)	5 (7.3)	6 (4.7)	
Poor	3 (1.5)	0 (0.0)	3 (2.4)	
Parent Health Compared to 1 year ago, n (%)				
Much Better	10 (5.1)	0 (0.0)	10 (7.9)	
Somewhat Better	32 (16.2)	13 (18.6)	19 (15.0)	0.0001*
About the Same	130 (66.0)	50 (71.4)	80 (63.0)	
Somewhat Worse	24 (12.2)	7 (10.0)	17 (13.4)	
Much Worse	1 (0.5)	0 (0.0)	1 (0.8)	

^ = Pearson Chi square test;

* = Fisher's exact test;

¥ = T-test

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Table 2

Child Clinical Characteristics

	All (n=198)	Responder (n=70)	Non- Responder (n=128)	p-value
Clinical Rett Syndrome, n (%)				
Yes	187 (95.0)	67 (95.7)	120 (94.5)	0.254 *
No	10 (5.1)	3 (4.3)	7 (5.5)	
Mutation, n (%)				
No Mutation	14 (7.2)	3 (4)	11 (9)	
Mutation Group 1				
R133C	11 (5.6)	5 (7)	6 (5)	
R294X	10 (5.1)	8 (11)	2 (2)	
R306C	15 (7.7)	7 (10)	8 (6)	
3' Truncation	9 (4.6)	4 (6)	5 (4)	
Mutation Group 2				
R106W	7 (3.6)	3 (4)	4 (3)	-
T158M	26 (13.3)	8 (11)	18 (14)	
Mutation Group 3				
R168X	22 (11.3)	4 (6)	18 (14)	
R255X	21 (10.8)	9 (13)	12 (10)	
R270X	10 (5.1)	2 (3)	8 (6)	
Large Deletion	11 (5.6)	3 (4)	8 (6)	
Mutation Group 4: “Others”				
Insertion	2 (1.0)	0 (0)	2 (2)	
Insertion/Deletion	2 (1.0)	2 (2)	0 (0)	
Other Point Mutation	33 (17.0)	12 (17)	21 (17)	
Duplication	2 (1.0)	0 (0)	2 (2)	
Average BMI, mean (SD)	18.2 (4.3)	19.6 (5.4)	17.4 (3.3)	0.004 ¥
Average Child Age, mean (SD)	13.7 (9.3)	16.4 (10.5)	12.3 (8.3)	0.015#
Average Age at Diagnosis, mean (SD)	3.5 (3.6)	4.6 (5.3)	2.9 (2.0)	0.009 ¥
CSS, mean (SD)	22.9 (7.6)	22.1 (7.8)	23.4 (23.4)	0.261 ¥
MBA (Behavioral/Social) , mean (SD)	20.4 (7.9)	19.8 (7.1)	20.8 (8.3)	0.391 ¥
MBA(Motor Assessment Physical), mean (SD)	17.2 (6.3)	17.1 (6.9)	17.2 (5.9)	0.900 ¥
MBA (Orofacial/Respirator), mean (SD)	6.9 (2.5)	7.3 (2.5)	6.7 (2.5)	0.123 ¥
MBA Total, mean (SD)	44.5 (13.1)	44.2 (12.9)	44.7 (13.3)	0.804 ¥

^ = Pearson Chi square test;

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[*] = Fisher's exact test;

[¥] = T-test;

[#] =Wilcoxon two-sample test

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Table 3

Pearson correlations with RTT CIA total score (n=198)

	Correlation	p-value
Parent age	−0.016	0.826
Parent General Health	0.379	<0.0001
Parent Health Compared to 1 year ago	0.244	0.001
BMI	0.086	0.240
Child Age	−0.043	0.553
Age at Diagnosis	−0.081	0.260
CSS	0.078	0.282
MBA (Behavioral/Social)	0.042	0.567
MBA(Motor Assessment Physical)	0.065	0.371
MBA (Orofacial/Respirator)	0.003	0.965
MBA Total	0.056	0.437

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Table 4

Average (SD) RTT CIA associated with demographic and clinical characteristics

	All (n=198)	p-value
Clinical Rett Syndrome		
Yes	61.7 (14.6)	0.266
No	67.0 (15.1)	
Mutation,		
No Mutation	69.6 (14.2)	
Mutation Group 1	61.2 (17.4)	0.024
Mutation Group 2	58.5 (11.9)	
Mutation Group 3	59.6 (12.9)	
Mutation Group 4	66.0 (15.0)	
Child Age Group (years)		
0–10	63.4 (13.5)	0.137
11–20	58.8 (12.4)	
>20	63.2 (18.7)	
CSS		
≤21	61.3 (14.1)	0.698
>21	62.1 (15.1)	
MBA Total		
0–30	57.6 (11.9)	0.193
31–50	61.7 (15.6)	
>50	63.8 (13.7)	0.175
Parent Gender		
Female	63.1 (13.8)	
Male	60.2 (15.7)	
Parent General Health		
Excellent	55.2 (13.2)	
Very Good	60.8 (12.6)	<0.0001
Good	67.8 (15.0)	
Fair	78.5 (15.7)	
Poor	63.7 (11.5)	
Parent Health Compared to 1 year ago		
Much Better	56.3 (11.1)	
Somewhat Better	61.8 (16.1)	<0.0001
About the Same	59.5 (12.5)	
Somewhat Worse	76.1 (15.7)	
Much Worse	77.0 (-)	

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Table 5

Exploratory Factor Analysis Factor Loadings (n=177)

Item		Factor Loading	Name of Factor
12	My health has been suffering.	0.803	Physical burden
13	Care giving has been making me physically sick.	0.746	
14	I'm always physically tired.	0.649	
9	My social life has been suffering.	0.610	
11	I haven’t been getting enough sleep.	0.555	
10	I feel emotionally drained due to caring for her.	0.525	
25	Although it is a challenge, raising my daughter also brings me great satisfaction.	0.635	Emotional burden
24	I feel angry about my interactions with her.	0.618	
22	I feel embarrassed over her behavior.	0.613	
23	I feel uncomfortable when I have friends over.	0.583	
7	I feel that I have been missing out on enjoyable activities.	0.573	
21	We have not been able to take our daughter out for dinner or other enjoyable activities because of her behavior and problems.	0.563	
8	I have been wishing that I could escape from this situation.	0.544	
26	I have had experiences recently that have given me hope.	0.501	
17	I've been having problems with my marriage (or other significant relationship).	0.659	Social burden
16	My care giving efforts aren't being appreciated by others in my family.	0.649	
15	I have not been getting along well with other family members.	0.644	
18	I have not been getting along as well as I used to with others.	0.634	
19	I have been feeling resentful of other relatives who could but do not help.	0.475	
5	I don't have a minute's time to myself.	0.563	Time Dependence
3	I have to watch her constantly.	0.497	
1	I don’t have time to perform any tasks for the family.	0.456	
4	I don’t have time to spend with other family members.	0.452	
20	I haven’t been able to pay as much attention to my relationship with other family members, including my daughter’s siblings (if there are other children in the family).	0.412	
2	She has been completely dependent on me for all her daily functions.	0.399	
6	I have needed to depend on a caretaker/aide/relative to help me with the care of my daughter.	0.265	