Pediatric Neurology 100 (2019) 80–86

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

A New Scale to Evaluate Motor Function in Rett Syndrome: Validation and Psychometric Properties

Marina Luisa Rodocanachi Roidi, MD [a], Ioannis Ugo Isaias, MD, PhD [b], Francesca Cozzi, BSc [a], Francesca Grange, BSc [a], Fabrizia Maria Scotti, MD [a], Valentina Francesca Gestra, BSc [a], Alessandra Gandini, BSc [a], Enrico Ripamonti, PhD [a, *]

[a] IRCCS Fondazione Don Carlo Gnocchi, Milano, Italy
[b] Department of Neurology, University Hospital Würzburg, Würzburg, Germany

ARTICLE INFO

Article history:
Received 7 October 2018
Accepted 6 March 2019
Available online 16 March 2019

Keywords:
Rett syndrome
Motor function
Validity
Reliability
Latent class analysis
Confirmatory factor analysis

ABSTRACT

Background: We aim to describe and psychometrically validate the Rett Syndrome Motor Evaluation Scale, a 25-item ordinal scale examining (loco-)motor function across six sections: standing, sitting, transitions, walking, running, and walking up or downstairs.
Methods: We illustrate the process of item construction and validation, report findings and normative data obtained on a standardization sample of 60 patients with Rett syndrome. We investigate the validity and reliability of the scale and illustrate its psychometric properties using modern multivariate techniques of data analysis.
Results: Sixty patients with Rett syndrome were included (all female; mean age 12.45 (S.D. 8.75) years). The multidimensional latent structure of the scale was supported by the results of the confirmatory factor analysis. Rett Syndrome Motor Evaluation Scale showed strong internal consistency reliability as well as excellent inter-rater agreement. The Rett Syndrome Motor Evaluation Scale scores were not predicted by age, but were associated with disease severity, degree of spasticity, and hand dysfunction. We also identified three latent classes with different degrees of impairment.
Conclusions: Rett Syndrome Motor Evaluation Scale is a new, valid, and reliable scale that can be introduced in clinical practice when assessing (loco-)motor function in Rett syndrome.

Introduction

Motor dysfunction is one of the most disabling components in patients diagnosed with Rett syndrome (RTT).[1] RTT is a rare pediatric neurological disease with an estimated incidence in the range of 1 in 9000[2] to 10,000[3] live female births. Generally, child development is apparently within the normal range in the first six months of life; regression starts at six to 18 months with loss of purposeful hand skills; stereotypic hand movements such as wringing, washing, or clapping; absent or dyspraxic gait; and loss of communication.[4] The clinical course of the disease and the hallmarks of the phenotype have been clearly described by the National History Study, the largest cohort study on RTT, following up for seven years 542 girls with typical RTT and 96 girls with atypical RTT.[5,6] This study documented the possible presence of abnormalities and failures, as well as developmental delay and prodromal signs already in the first six months of life of individuals with RTT.[7,8]

Gait and posture can be particularly impaired in RTT at different stages of disease and with different degrees of severity.[9,10] For instance, Downs et al.[11] showed that about 37% of their participants were unable to walk and the most common related mutations were early truncating or p.Arg168, and in smaller proportion, C-terminal deletion, p.133Cys, p.Arg306Cys, or p.Arg294 mutation of the MECP2 gene. Other authors reported that walking abilities would be relatively preserved in C-terminal deletions[2] and impaired in T158M, R106W, R255X, and R270X mutations.[12] A genotype-phenotype correlation study with a large sample of patients (more than 1000) showed that large deletions, splice sites, p.Arg270X, and p.Arg.168X are more frequently associated with locomotion impairment.[13] Children with RTT present a typical

Conflicts of interest: None reported.

* Communications should be addressed to: Ripamonti; IRCCS Fondazione Don Carlo Gnocchi; Via Alfonso Capecelatro, 66; Milano 20148, Italy.
E-mail address: enrico.ripamonti@unimib.it (E. Ripamonti).

https://doi.org/10.1016/j.pediatrneurol.2019.03.005
0887-8994/

pattern of abnormal or delayed (loco-)motor function[14] that have been described in detail by Nomura and Segawa.[15-17] In particular, some patients start walking without ever crawling, whereas others present both delayed crawling and delayed walking. In general, independent walking is maintained in about 50% of girls with RTT, and an additional 20% walk with some measure of assistance. In this situation gait is usually irregular, uncoordinated, and characterized by a wide-based posture, rocking of the trunk, toe walking, and retropulsion. Even if crawling and gait are initially possible, some patients may lose these capabilities during the regression phase or after the regression period.[10]

Available clinical scales do not comprehensively capture these idiosyncratic features, or the variability of presentation of gait and postural abnormalities. Bayley scales[18] contain a motor evaluation section consisting of fine and gross motor subtests. Even though it has also been used to evaluate RTT,[19,20] the motor part of these scales is not specific for this neurological disorder. The large standardization sample, made up of 1700 children (aged one to 42 months), comprised only 10% of children with physical, mental, or behavioral problems and may not have included children with RTT. Griffiths scales[21] comprise a scale of gross motor functioning, but again do not seem specific to assess the peculiar patterns of (loco-)motor derangements in RTT. In addition, the standardization sample included children aged zero to 72 months and, similar to the standardization sample of the Bayley scales, is not appropriate to test older children or adolescents.

There is also another motor scale specific for RTT and already validated: the Rett Syndrome Gross Motor Scale (RSGMS).[22,23] However, in our opinion this scale does not describe sufficiently the difficulties of RTT children during gait or postural changes (e.g., postural transitions, walking up or downstairs). A proper evaluation of gait and posture derangements is important for an early and appropriate intervention and follow-up.

In this general framework, we targeted the clinical need for a reliable tool to specifically evaluate (loco-)motor function in patients with RTT and defined a new clinical scale, the Rett Syndrome Motor Evaluation Scale (RESMES). The RESMES items are centered on the International Classification of Functioning[24] construct of patients' capacity, which reflects what an individual can do in a semistandardized environment, and has been conceived to capture fine-grained characteristics of movement. We aim to describe this new scale and the process of item construction and validation, and to provide standard criteria and norms for score interpretation.

Methods

Participants

Patients diagnosed with RTT participated in this study. We included only patients aged three years and older with a diagnosis of typical RTT, following the guidelines by Neul et al.,[4] and with a positive *MECP2* genetic test. Patients with impairment of psychomotor functions in the first six months of life or with neurometabolic diseases, cerebral infection, or encephalic damage secondary to perinatal trauma were also excluded. Parents or legal guardians provided a written informed consent to participate in this study. All procedures were in agreement with the Helsinki declaration and the study protocol was approved by the local Ethical Committee.

Medical evaluation

Girls underwent an extensive and detailed neurological examination (of cranial nerves, sensory and motor responses including reflexes, etc.) and assessment of the musculoskeletal components of the limbs and trunk. As X-ray images were not standardized (patients could be supine, seated, or standing, depending on disease severity and on compliance during the examination), the presence of scoliosis was codified with a scale already used to classify scoliosis in cerebral palsy[25,26] (see Supplementary Information).

RESMES scale: general principles

Motor function was tested by two neurodevelopmental therapists (with three years of experience in the evaluation of RTT) and two physicians (M.L.R.R. and F.M.S.) with specific competence in pediatric neurology and rehabilitation. Evaluators first completed RESMES, a 25-item scale investigating patients' (loco-) motor performance across six sections: (1) standing, (2) sitting, (3) transitions, (4) walking, (5) running, and (6) walking up or downstairs (see the Supplementary Information). Sixteen items are rated on a 0 to 4 scale, where 0 indicates null or very mild impairment and 4 indicates severe impairment; nine items relative to walking abilities are rated on a 0 to 2 scale. This scale has been specifically developed to capture motor dysfunction in patients with RTT and can be completed either during formal assessment or subsequently while watching a video of the evaluation session. A necessary condition to administer the scale is the exclusion of pain or other symptoms such as fever, coughing, or flu. Movement examination with the RESMES scale lasts from 40 minutes to one hour, mostly according to the patient's compliance, and takes place in a single session in a large and comfortable room, equipped with toys. A detailed description of the RESMES scale, its clinical utility, and a comparison between evaluation by the neurologist in a clinical outpatient setting and scoring performed by caregivers in a home environment is the topic of a separate and complementary article.[27]

Other clinical scales

Clinicians also completed (1) the modified Ashworth scale,[28] to assess the degree of spasticity of the four limbs; (2) a scale of evaluation of purposeful hand functioning[29,30]; and (3) the Pain Assessment in Advanced Dementia scale,[31] to exclude the concomitant presence of painful symptoms during assessment. Rett Assessment Rating Scale (RARS) evaluations,[32] provided by parents, were available for each patient. The RARS offers a composite score, calculated from 31 items, each assessed on a 1 to 4 ordinal scale; RARS assesses six domains, namely, (1) cognition, (2) sensory system, (3) motor system, (4) emotions and affects, (5) daily life autonomy, and (6) typical RTT features.

The evaluation of muscle tone is difficult in RTT, particularly in the first decade of life. These girls may not relax easily and often oppose to the joint mobilization a voluntary movement. In this case, we first waited for the patient to get more acquainted with the room and surroundings and to be more relaxed. We often used a tablet showing the favorite cartoon or music. We also distracted the child with live music (a guitar player). This helped to attain a more comfortable condition for the clinical evaluation. The Ashworth's maneuvers were carried out only when a state of maximum relaxation was achieved. In addition, the evaluation of the osteotendinea reflexes (see “medical evaluation”) helped distinguishing spastic and plastic hypertonia, the latter present only in a few isolated patients older than 18 years. In this case, patients were not considered positive with the Ashworth's scale. Of relevance, to be consistent among visits the same two physicians (M.L.R.R. or F.M.S.) evaluated all patients.

RESMES scale: items construction and validation process

In an initial phase, the general construction principles of the new scale, referred to as gait analysis and developmental neurology, were established; i.e., the authors decided the type of components of movement and which aspects would have been necessary to test. A core principle of scale construction was that it had to be applied along a full range of severity of movement impairment and across different ages. The first version of the RESMES scale was prepared by M.L.R.R., and I.U.I and discussed with other colleagues who were expert in RTT, as well as with parents and caregivers, to address the main (loco-)motor limitations in RTT. Consensus was achieved on a short list of 25 items, and a pilot version was tested in 35 patients followed up for 12 months. This preliminary observation period allowed improvement of the scoring system to better describe the severity of each symptom. For the present study, only the final version of RESMES was used in a recruitment period of three years (2014 to 2017).

Descriptive analysis

Data were analyzed using descriptive indicators such as mean (S.D.), median, interquartile range, confidence intervals (C.I.), and correlation coefficients. Once completed, the scale scores for each item can be summed, thus giving a total RESMES score (range: 0 to 82). This score can be transformed into the corresponding normalized T score and stanine score (see Supplementary Table S1). The latter may provide an indication on motor dysfunction severity: indeed, stanine values of 1 to 2, 3 to 4, 5 to 6, and 7 to 9 would correspond, respectively, to a level of minimal (or null), mild, moderate, and severe impairment, respectively.[33] The normal distribution of the total RESMES scores was preliminarily checked using a Kolmogorov-Smirnov test.

Internal consistency reliability

We first estimated internal consistency reliability by calculating split-half reliability, namely, splitting in half the scale and correlating the two halves[34] (see the Supplementary Information). Second, we calculated Cronbach alpha coefficient, which is another classical measure of internal consistency.

Inter-rater agreement

Five neurodevelopmental therapists, who were not included in the formal assessment of patients but who had specific experience in RTT, independently rated RESMES scores of videos of the motor functions of eight patients chosen randomly in the data set. All three therapists received from physicians precise instructions on the RESMES scale and its scoring system. To verify the inter-rater agreement, we calculated the s* statistic using linear weights.[35] This measure is founded upon a procedure that is not affected by paradoxes of Fleiss' *kappa*.[36]

Confirmatory factor analysis

Confirmatory factor analysis (maximum likelihood estimation) has been used to verify the construct validity of the RESMES scale, i.e., the possibility of six latent dimensions of motor function to be separately evaluated in RTT. Modification indices have been used to free or fix parameters related to variances or covariances of endogenous variables, and comparative fit index, Tucker-Lewis index, root mean square error of approximation, and standardized root mean squares of residuals indices have been adopted to assess model fit.

Multidimensional latent class item response theory models

We further investigated latent traits by running a multidimensional latent class item response theory (IRT) model,[37] which is an extension of the traditional IRT models that have been developed in cases of binary responses and ordinal polytomous items.[38] Statistical details are provided in the Supplementary Information.

Multiple regression analysis

We used multiple regression to verify the association of RESMES scores with those obtained on other clinical scales, namely, RARS, Pain Assessment in Advanced Dementia, Ashworth, hand functioning, and scoliosis.

Statistical software

All analyses were run with R software. In particular, the package multicon was used for split-half reliability, and the package raters, for the analysis of inter-rater agreement. As for the latent variable analyses, the package lavaan was used for factor analysis and the package MultiLCIRT was adopted for latent class analysis. A nominal value of 0.05 was set to evaluate the significance of each *P* value. No adjustment for multiple comparisons was needed for these analyses.

Clinical illustration

In the Supplementary Information, we describe two individuals and their motor function evaluation using the RESMES scale; two video clips are also available.

Results

Descriptive analysis

Sixty patients diagnosed with RTT participated (all female; mean age 12.45 [S.D. 8.75] years, median age 10 years, range: 3 to 40 years). It was possible to administer the RESMES scale to all of them. In Table 1, we show the mean (S.D.) performance of participants in each of the six sections of the RESMES scale; medians and interquartile range are also reported.

The mean RARS score was 65.86 (S.D. 8.9, median 65, range 47 to 89), indicating, on average, moderate impairment. Genotype analysis indicated that we had eight patients with carboxy-terminal mutation, nine with large deletions, 20 with mutation in the transcription repression domain (TRD), 15 with mutation in the methyl-binding domain, one with amino-terminal mutation, and seven with other types of mutations. In Table 2 we reported mean RARS scores and average RESMES scores by type of mutation.

We observed that, on average, the impairment was mild for the standing and sitting sections, but moderate or severe for transitions, walking, running, and going up or downstairs. Autonomous walking (i.e., the ability to walk alone for at least 11 steps without assistance, item D14 of the RESMES scale) was present in 26 of 61 patients (42.6%). To evaluate the degree of impairment of motor function, we transformed RESMES total scores into both standard T scores and stanine scores (see Supplementary Information). Scores below 17 indicate minimal or no deficit. A Kolmogorov-Smirnov test on Total RESMES scores did not reject the hypothesis of normal distribution ($D = 0.09$, $P = 0.69$).

TABLE 1.
Descriptive Statistics (Mean, S.D., Median, Interquartile Range) for Each of the Six Sections of the RESMSES Scale

	Range	Mean	S.D.	Median	Interquartile Range	α
Standing	0-4	1.31	1.67	0	3	0.86 [0.80-0.92]
Sitting	0-4	0.99	1.23	1	1	0.78 [0.75-0.80]
Transitions	0-4	2.11	1.26	2	1	0.89 [0.85-0.93]
Walking	0-2	1.11	0.90	1	2	0.96 [0.94-0.97]
Running	0-4	3.65	0.99	4	0	–
Stairs	0-4	3.08	1.07	3	2	0.93 [0.90-0.96]

Abbreviation:
RESMES = Rett Syndrome Motor Evaluation Scale
We also report the Cronbach α coefficient (with the confidence interval in brackets) for each section, with the exception of the section "Running," which is made up of one item only.

In Table 3, we show the correlation coefficients between T scores of different RESMES sections. Walking abilities highly correlated with standing ($r = 0.81$), walking up or downstairs ($r = 0.64$), and transitions ($r = 0.70$), whereas correlations were low with sitting and running. Moderate to strong correlations emerged for the section transitions with all other sections, whereas sitting proved to be an independent dimension.

Internal consistency reliability

We estimated a mean split-half correlation coefficient of 0.92; adjusting using the Spearman-Brown formula, we obtained a split-half reliability coefficient of 0.96 (S.D. 0.18). We also estimated the Cronbach alpha coefficient for the entire scale, $\alpha = 0.95$ (CI 0.93–0.97), and separately for each section, excluding running (see Table 1). These results indicate a very good internal consistency of the RESMES scale; in particular, the high α coefficient demonstrates remarkable homogeneity across items.

Inter-rater agreement

We obtained very high values of the s^* statistic, and all were statistically significant; this indicates optimal inter-rater agreement among clinicians. Detailed results of this analysis, including t-bootstrap CI and Monte Carlo P values for the s^* statistic, are reported in Table 4.

Confirmatory factor analysis

We estimated a confirmatory factor analysis model through maximum likelihood, inserting the six sections of the RESMES scale as latent variables, i.e., unobserved variables.[39] After adjustments on the variance or covariance parameters using modification indices, the final model had a good fit: comparative fit index = 0.95, Tucker-Lewis index = 0.94, root mean square error of approximation = 0.08, standardized root mean squares of residuals = 0.10. Parameter estimates and tests of significance are shown in Supplementary Table S2. These results support the foundation of a six-dimensional latent structure underpinning RESMES items.

Multidimensional latent class IRT models

To estimate multidimensional latent class IRT models, we first determined the optimal number of latent classes. Using a Bayesian information criterion (the smaller the better), we detected that three latent classes represent an optimal solution (see the Supplementary Information). A global logit link was preferred to a local logit link or to the classical latent class model; we also rejected the hypothesis of unidimensionality (likelihood ratio test, $P < 0.0005$). Under these assumptions, we estimated a final model, which indicates that motor function in RTT can be adequately described postulating three latent classes with different degrees of severity of impairment (across all six dimensions). Patients have a probability of 0.20 of belonging to the first class (least severe condition), 0.41 of belonging to the second class (intermediate condition), and 0.39 of belonging to the third class (most severe condition, see Table 5).

Multiple regression analysis

We estimated a multiple regression model inserting Total RESMES score as dependent variable and age, pain level, Total RARS scores (as an index of disease severity), Ashworth scores, hand functioning, and degree of scoliosis as regressors. Results showed that neither age nor pain predicted RESMES scores; these were associated with Total RARS scores ($\beta = 0.52(0.23)$, t = 2.17, $P = 0.03$), Ashworth scores ($\beta = 0.58(0.24)$, t = 2.43, $P = 0.02$), and hand functioning ($\beta = -1.80(0.57)$, t = −3.15, $P = 0.002$). There was a

TABLE 2.
Average RARS scores (as Marked by Parents) and Clinical RESMES Scores (Total, Standing, Sitting, Walking, Transitions) by Type of Mutation

Mutation	RARS	RESMES				
		Total	Standing	Sitting	Walking	Transitions
C-terminal (n = 8)	66.1	23.7	0.5	0.6	0.1	9.6
Large deletion (n = 9)	63.2	45.2	2.9	1.0	1.3	16.0
TRD (N = 20)	67.4	44.5	2.4	1.5	1.1	15.5
MBD (N = 15)	62.1	38.7	1.9	0.7	0.9	14.7
N-terminal (N = 1)	73	55.5	4.0	1.0	2.0	19.0
Other (N = 7)	72.1	44.3	2.4	1.0	1.1	16.1

Abbreviations:
MBD = Methyl-binding domain
RARS = Rett Assessment Rating Scale
RESMES = Rett Syndrome Motor Evaluation Scale
TRD = Transcription repression domain

TABLE 3.
Correlations (Pearson's Method) Between T Scores of Different Subsections of the RESMES Scale, and Correlations With Age

Variable	Age	Standing	Sitting	Transitions	Walking	Running	Walking Up/Downstairs
Age	1						
Standing	−0.15	1					
Sitting	0.23	0.33	1				
Transitions	0.20	0.56	0.45	1			
Walking	−0.14	0.81	0.31	0.70	1		
Running	−0.04	0.30	0.12	0.51	0.46	1	
Stairs	−0.23	0.64	0.26	0.69	0.77	0.48	1

Abbreviation:
RESMES = Rett Syndrome Motor Evaluation Scale

trend on the association of RESMES scores with the degree of scoliosis ($\beta = 3.13$ (1.84), t = 1.69, $P = 0.09$).

Discussion

The objective of our study was to describe the psychometric properties of the RESMES scale, a new scale for the specific evaluation of (loco-)motor deficit in RTT. The items of the scale and the validation process were discussed, and normative data on the Total RESMES score, collected on a standardization sample of 60 patients with RTT, were introduced. Six areas of motor function are examined by RESMES, i.e., standing, sitting, transitions, walking, running, and walking up or downstairs. The RESMES is a scale intended specifically for a fine-grained evaluation of balance and gait derangements in RTT, with reference to the capacity construct of the International Classification of Functioning, Disability and Health.[24] Given the difficulty of correctly assessing the true (loco-) motor capabilities of patients with RTT in an outpatient clinic environment, the RESMES scale was intended to be used also in home environment (by caregivers).[27] In this context, the RESMES allows for a clear assessment of the level of autonomy of the patient, as it takes into account the degree of assistance required by the patient to complete the task (e.g., standing unassisted or held by one or two hands). We envisioned that the RESMES could be a valuable tool for clinicians and physical therapists to tailor therapies on the specific needs of the patient and families.[40,41] This scale could also help to follow-up the progression of (loco-)motor function, targeting patients at risk of losing these capabilities. As other scales (e.g., the Berg scale[42] and the Tinetti scale[43]) the RESMES was constructed in a severity step-by-step assessment. An example, at item A1, a score 0 to 3 excludes A2 and A3, thus reducing the time needed to complete the scale.

TABLE 4.
Results of the Analysis of Inter-rater Agreement Among Five Independent Clinicians Who Evaluated Video Clips of the RESMES Scale of Eight Different Patients.

Patient	s^*	Confidence Intervals		P value
		LB	UB	
Patient 1	0.81	0.71	0.90	<0.0005
Patient 2	0.85	0.75	0.93	<0.0005
Patient 3	0.87	0.80	0.93	<0.0005
Patient 4	0.80	0.71	0.88	<0.0005
Patient 5	0.70	0.56	0.83	<0.0005
Patient 6	0.78	0.67	0.86	<0.0005
Patient 7	0.75	0.65	0.84	<0.0005
Patient 8	0.84	0.78	0.90	<0.0005

Abbreviations:
LB = Lower bound
RESMES = Rett Syndrome Motor Evaluation Scale
UB = Upper bound
We show the values of the s^* statistic, bootstrap confidence intervals, and Monte Carlo P values.

The RESMES differs from the RSGMS in many ways. (1) RESMES considers the possibility of nonacquisition of a motor competence (whereas RSGMS would score "maximal assistance" if the item was completed passively); (2) for static items, such as standing or sitting, RESMES requires an evaluation of 60 seconds, rather than only 10 or 20 seconds as in the RSGMS, thus providing more valuable information from a rehabilitative and ecological perspective; (3) RESMES evaluates the sitting position both with feet touching the ground and with feet raised from the ground, which is very important to examine balance of the trunk; (4) with respect to gait, RESMES assesses whether it is possible without assistance or held by one or two hands; (5) RESMES introduces an evaluation of the possibility of stepping over two obstacles and of walking up or downstairs, which is very important for everyday life; (6) transitions are examined in much more detail by RESMES than RSGMS, starting from rolling supine to one side and rolling supine to prone. This comprehensive assessment of transitions would offer valuable clinical information on the autonomy level of girls, which should be the main goal of rehabilitation strategies.

Results of group analyses presented in this article indicated that patients whose motor function had been examined with RESMES had, on average, a relatively different performance across different sections of the scale. Running and going up or downstairs were severely impaired, whereas sitting was relatively preserved. Sitting emerged as a relatively uncorrelated dimension, whereas walking was highly correlated with standing and transitions. Age was not associated with the RESMES score, thus normative data illustrated in the Supplementary Information did not have to be adjusted by age. We also calculated the correlation scores of each of the RESMES subsections with age, but Pearson's coefficients indicated the presence of low correlation only. A similar result has been reported by Downs et al.,[22] who found that skills such as stepping over an obstacle or running did not correlate with age (their sample was made of 99 girls from the Australian Rett Syndrome Database, median age = 14.1 years, range = 1.5 − 27.9 years). However, the authors also found that skills such as standing or sitting did correlate with age, which deserves further investigation in large

TABLE 5.
Multidimensional Latent Class Item Response Theory Model

	Class 1	Class 2	Class 3
Dimension 1	−17.41	−1.69	−3.07
Dimension 2	−2.52	−2.22	−1.13
Dimension 3	−1.63	0.75	2.50
Dimension 4	−6.58	−0.39	4.63
Dimension 5	0.31	3.40	18.47
Dimension 6	0.89	1.94	19.12
Probability	0.20	0.41	0.39

Parameter estimates and probability of belonging to each of the latent classes.

samples of patients. FitzGerald et al.[44] tested several dimensions of movement as captured by the Rett Syndrome Motor Behavioral Assessment scale (e.g., hand clumsiness, ataxia, dystonia, etc.) and divided patients into three groups according to age (less than four years, four to eight years, and greater than eight years), but "a statistically significant difference in the occurrence of the various movement disorders between the groups was found only for hypomimia ($P < 0.05$), which was more common and more severe in older patients" (p. 197). We may suggest that these negative results reflect the heterogeneity of presentation of patients with RTT, and thus the issue of ascertaining the association of age with motor function is open for future research.

Results from multiple regression analyses indicated that Total RESMES scores were associated with disease severity (as measured by the Total RARS scores) and with the degree of spasticity and hand functioning. A trend also emerged as to the association between the Total RESMES score and the degree of scoliosis.

The theoretical premise of this study, which motivated the creation of a new scale, was that motor function in RTT is a multidimensional construct and, given the large phenotype heterogeneity, different dimensions such as walking, running, or stepping over obstacles could be differently impaired. A latent structure made up of six dimensions has been supported by the results of the confirmatory factor analysis and multidimensional latent class IRT analysis. The RESMES also proved to have very high internal consistency reliability, as indicated by the split-half and α reliability coefficients.

Inter-rater agreement is a very important property that should be satisfied by a new clinical scale. Indeed, agreement among clinicians with similar degree of expertise implies stability of the scores as well as uniformity in medical evaluation and scale use. We validated the RESMES scale using the s^* statistic,[35,36] which does not suffer from the same drawbacks of the *kappa* statistic[35] and has straightforward statistical properties. In addition, Monte Carlo *P* values and bootstrap-t CIs can be calculated through a recent R package. Results presented herein demonstrate an excellent inter-rater agreement for the RESMES scale. Nevertheless, these results should be corroborated by prospective studies on a larger sample of girls with RTT.

Findings of the multidimensional latent class IRT analysis provided additional evidence as to the multidimensional latent structure of the RESMES scale. It was also shown that patients are optimally classified in three different latent classes, characterized by different degree of severity of motor function. Eighty percent of patients would belong to the classes described by intermediate or severe impairment, and this information should be worth considering when planning rehabilitative services.

The main limitation of this study was that the relatively small sample size for a validation study; for this reason, we did not conduct multivariable analyses segmenting the sample by genotype. However, all patients with RTT were evaluated by the same neurologists at the same center (same environment), thus significantly increasing the reliability of our findings. This was a cross-sectional study, hence test-retest reliability could not be calculated and will be assessed by future research. It is also open for future research the possibility of correlating the (loco-) motor function as assessed by RESMES, with the scores of the Rett Syndrome Motor Behavioral Assessment,[44] which offers a detailed evaluation of girls across several domains (i.e., behavioral/social assessment, orofacial/respiratory assessment, motor assessment/physical signs). In conclusion, the RESMES scale can be introduced into clinical practice and might supplement other scales for detailed (loco-)motor evaluation in patients with RTT.

Acknowledgments

This work was supported by grants from the Italian Ministry of Health, AIRETT, and Pierfranco and Luisa Mariani Foundation. We are grateful to Kumiko Toshimori for her assistance with the editing of the two video clips.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2019.03.005.

References

1. Neul J, Zoghbi H. Rett syndrome: A prototypical neurodevelopmental disorder. Neurosci. 2004;10:118–128.
2. Fehr S, Bebbington A, Nassar N, et al. Trends in the diagnosis of Rett syndrome in Australia. Pediatr Res. 2011;70:313–319.
3. Laurvick CL, De Klerk N, Bower C, et al. Rett syndrome in Australia: a review of the epidemiology. J Pediatr. 2006;148:347–352.
4. Neul J, Kaufmann W, Glaze D, et al. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol. 2010;68:944–950.
5. Neul J, Lane J, Lee H-S, et al. Developmental delay in Rett syndrome: data from the Natural History Study. J Neurodev Disord. 2014;6:20.
6. Percy A, Neul J, Glaze D, et al. Rett syndrome diagnostic criteria: lessons from the Natural History Study. Ann Neurol. 2010;68:951–955.
7. Tarquinio D, Motil J, Hou W, et al. Growth failure and outcome in Rett syndrome. Neurology. 2012;79:1653–1661.
8. Glaze D, Percy A, Skinner S, et al. Epilepsy and the natural history of Rett syndrome. Neurology. 2010;74:909–912.
9. Gold W, Krishnarajy R, Ellaway C, Christodoulou J. Rett syndrome: a genetic update and clinical review focusing on comorbidities. Chem Neurosci. 2018;9:167–176.
10. Leonard H, Cobb S, Downs J. Clinical and biological progress over 50 years in Rett syndrome. Nat Rev Neurol. 2017;13:37–51.
11. Downs J, Leonard H, Wong K, Newton N, Hill K. Quantification of walking-based physical activity and sedentary time in individuals with Rett syndrome. Dev Med Child Neurol. 2017;59:605–611.
12. Neul J, Fang P, Barrish J, et al. Specific mutations in Methyl-CpG-binding protein 2 confer different severity in Rett syndrome. Neurology. 2008;70:1313–1321.
13. Cuddapah V, Pillai R, Shekar K, et al. Methyl-CpG-binding protein 2 (MECP2) mutation type is associated with disease severity in Rett syndrome. J Med Genet. 2014;51:152–158.
14. Hagberg B. Clinical manifestations and stages of Rett syndrome. Ment Retard Dev Disabil Res Rev. 2002;8:61–65.
15. Nomura Y, Segawa M. Characteristics of motor disturbance in Rett syndrome. Brain Dev. 1990;12:27–30.
16. Nomura Y, Segawa M. Motor symptoms of the Rett syndrome: abnormal muscle tone, posture, locomotion and stereotyped movement. Brain Dev. 1992;14:S21–S28.
17. Segawa M. Early motor disturbances in Rett syndrome and its pathophysiological importance. Brain Dev. 2005:S54–S58.
18. Bayley N. Bayley scales of infant development. 3rd ed. San Antonio, TX: Pearson Education; 2006.
19. Moeschler J, Charman C, Berg S, Graham J. Rett syndrome: natural history and management. Pediatrics. 1986;82:1–10.
20. Oliver C, Murphy G, Crayton L, Corbett J. Self-injurious behavior in Rett syndrome: interactions between features of Rett syndrome and operant conditioning. J Autism Dev Disord. 1993;23:91–109.
21. Green E, Stroud L, Bloomfield S, et al. Griffiths scales of child development. 3rd ed. Oxford: Hogrefe; 2016.
22. Downs J, Bebbington A, Jacoby P, et al. Gross motor profile in Rett syndrome as determined by video analysis. Neuropediatrics. 2008;39:205–210.
23. Downs J, Stahlhut M, Wong K, et al. Validating the Rett syndrome gross motor scale. PLoS One. 2016;11:e0147555.
24. World Health Organization. The International Classification of Functioning, Disability and Health (ICF). Geneva: WHO; 2001.
25. Persson-Bunke M, Czuba T, Hagglund G, Rodby-Bosquet E. Psychometric evaluation of spinal assessment methods to screen for scoliosis in children and adolescents with cerebral palsy. BMC Musculoskelet Disord. 2015;16:351–356.
26. Persson-Bunke M, Hagglund G, Lauge-Pedersen H, Wagner P, Westbom L. Scoliosis in a total population of children with cerebral palsy. Spine Deform. 2012;37:E708–E713.
27. Rodocanachi Roidi M, Isaias I, Cozzi F, et al. Motor function in Rett syndrome: comparing clinical and parental assessments. Dev Med Child Neurol. 2018. https://doi.org/10.1111/dmcn.14109. Accessed December 29, 2018.
28. Bohannon RW, Smith M. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther. 1987;67:206–207.

29. Downs J, Parkinson S, Ranelli S, Leonard H, Diener P, Lotan M. Perspectives on hand function in girls and women with Rett syndrome. Dev Neurorehabil. 2014;17:210–217.
30. Downs J, Bebbington A, Jacoby P, et al. Level of purposeful hand function as a marker of clinical severity in Rett syndrome. Dev Med Child Neurol. 2010;52:817–823.
31. Warden V, Hurley AC, Volicer L. Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) scale. J Am Med Dir Assoc. 2003;4:9–15.
32. Fabio RA, Colombo B, Russo S, et al. Recent insights into genotype–phenotype relationships in patients with Rett syndrome using a fine grain scale. Res Dev Disabil. 2014;35:2976–2986.
33. Huber W, Poeck K, Weniger D, Willmes K. Der Aachener Aphasie Test (AAT). Göttingen: Hogrefe; 1983.
34. Kline P. Handbook of psychological testing. London: Routledge; 2000.
35. Marasini D, Quatto P, Ripamonti E. Assessing the inter-rater agreement for ordinal data through weighted indexes. Stat Methods Med Res. 2016;25:2611–2633.
36. Marasini D, Quatto P, Ripamonti E. The ordinal inter-rater agreement in the evaluation of university courses. Stat Appl. 2014;12:5–16.
37. Bartolucci F, Bacci S, Gnaldi M. MultiLCIRT: An R package for multidimensional latent class item response models. Comput Stat Data Anal. 2014;71:971–985.
38. Bartolucci F. A class of multidimensional IRT models for testing unidimensionality and clustering items. Psychometrika. 2007;72:141–157.
39. Loehlin J. Latent variable models: An introduction to factor, path, and structural analysis. 3rd ed. Mahwah, NJ: Lawrence Erlbaum Associates Publishers; 1998.
40. Rosenbaum P, King S, Law M, King G, Evans J. Family-centred service: A conceptual framework and research review. Phys Occup Ther Pediatr. 1998;18:1–20.
41. King G, King S, Rosenbaum P, Goffin R. Family-centered caregiving and well-being of parents of children with disabilities: linking process with outcome. J Pediatr Psychol. 1999;24:41–53.
42. Berg K, Wood-Dauphinee S, Williams J, Gayton D. Measuring balance in the elderly: Preliminary development of an instrument. Physiother Can. 1989;41:304–311.
43. Tinetti M. Performance-oriented assessment of mobility problems in elderly patients. J Am Geriatr Soc. 1986;34:119–126.
44. FitzGerald P, Jankovic J, Percy A. Rett syndrome and associated movement disorders. Mov Disord. 1990;5:195–202.