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Gross Motor, Physical Activity and Musculoskeletal Disorder Evaluation Tools for Rett Syndrome: A Systematic Review

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ABSTRACT

In recent years, much attention has been paid to motor impairment of persons with Rett Syndrome (RTT), with increasing literature aimed to describe gross motor functioning and musculoskeletal disorders of the RTT population. The aim of this systematic review is to describe clinical evaluation tools used in the last decade to assess motor functioning and musculoskeletal abnormalities of patients with RTT. Thirty-four studies were reviewed and 20 tools were presented. Results showed that only two tools were used to measure functional change after rehabilitative or therapeutic interventions. This review underlies the lack of adequate evaluation tools to assess musculoskeletal abnormalities and deformities in RTT population. The absence of these assessments could be due to a statistical difficulty as it is challenging to build an evaluation tool that can score the entities of the abnormalities related to the amount of disability they cause.

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KEYWORDS
Rett syndrome; motor assessment; gross motor functioning; physical activity; musculoskeletal disorder; evaluation tools

Introduction

Rett syndrome (RTT) is a severe neurodevelopmental disorder affecting almost exclusively young girls. In the majority of cases it is caused by the mutated MeCP2 gene, encoding the Metil-CpG binding 2 protein, on the long arm of the X chromosome.[1,2]

Affected girls usually show normal or slightly delayed development in the first 6–18 months followed by a developmental stagnation and subsequent regression of acquired skills.[3–7] Regression occurs between first and fourth years of life and is characterized by a pervasive loss or functional reduction of the acquired gross-motor and communication skills and by the replacement of purposeful hand use with repetitive and stereotyped movements.[3,5] After regression, a prolonged period of stabilization occurs with reported improvement in social interaction, eye contact, and socialization contrasting with a gradual decrease of motor functioning marked by increasing muscle tone, rigidity, and dystonic posturing, particularly of the feet, hands, and occasionally, the trunk.[8–11]

Gross motor function in RTT is almost always limited.[12] In the regression phase, patients begin to develop defects in coordination and instability that occur with uncontrolled movements of the body segments and partial loss of trunk and balance control.[3,4,13–16] Residual gross motor functions are usually preserved till adulthood, with the majority of patients being able to walk with support and almost half who can walk independently or with minimal support.[8,17] Deambulation occurs with skewed sensory processes (apraxia), fluctuating muscle tone, and poor coordination.[18] More complex motor abilities such as climbing or descending stairs are usually poor and only few girls can perform them independently. Apraxia makes postural changes difficult although more than half of the girls can sit and stand from a chair and slightly less than half are able to get in and out from bed without using their arms.[17] Previous studies reported a decrease in motor functioning quality and level from the age 13 with a progressive increase in the support needed to complete motor tasks.[8,17] Moreover, fluctuation in muscle tone has been reported from late childhood[18] together with appearance of parkinsonism rigidity.[19] In the RTT population, the differences in severity of motor disability, pattern of neurology and degree of impairment are striking and various[20] with several different clinical pictures presenting between subjects.

Associated to neuromuscular impairment, the development of musculoskeletal abnormalities has been reported in RTT syndrome. Deformities of spine and feet are prevalent although all body joints can be affected.[21] In a large study which included 909 females with RTT aged between 1 and 66 years, the presence of scoliosis has been reported in 80% of the enrolled subjects over 13 years of age.[22] Moreover, an Italian study which screened 84 subjects with RTT aged between 14 and 42 years recognized joints deformities in36% of the included patients with RTT.[23]Genotype-phenotype correlations with specific motor abilities and type of MECP gene mutation have been detected in RTT. The most severe mutations include Arg270X, Arg255X, and Arg168X which have been related to early symptoms soon after birth and more delayed developmental milestones achievement such as walking. In contrast, mutations Arg133Cys, Arg294X, and C-terminal deletions are associated with less-severe phenotypes and better ambulatory skills.[16,24–28]

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Furthermore, the acquisition of early developmental milestones appears to be influenced by other mutations, such as p.R255X, p.R168X, p.R270X, or early truncating mutations. The age of regression also varied by mutation type. Girls who had a C-terminal deletion or a p.R133C mutation had a later onset of regression, while girls with p.R168X, p.R270X, p.R255X, and p.T158M mutations showed earlier regression.[29]

As shown, the motor function picture of RTT is highly complex and appears to be multifactorial. RTT is a particularly challenging disorder even for highly trained rehabilitation therapists, with respect to severity of motor and cognitive impairment, osteotendinous retractions, and progressive immobility, which characterize the later stages of the disease.[8] Lifelong rehabilitation intervention should be performed to maintain individuals with RTT as functional as possible accompanying the person through the disease evolution and stages.[10,30] To perform adequate and effective treatment, rehabilitation therapists should rely on previous accurate evaluation of the girls' functioning, characteristics, environment, and clinical status. The rehabilitative evaluation process should be aimed to set rehabilitative goals and to determine individual and environmental strengths and weaknesses that can be exploited or dealt with by therapeutic intervention to improve the quality of life of the patient and the family.[30]

In recent years, much attention has been paid to motor impairment of persons with RTT, with increasing literature aimed to describe gross motor functioning and musculoskeletal disorders of the RTT population. This has been accompanied by the creation and use of a variety of evaluation tools to assess various motor and postural manifestations of RTT. The aim of this systematic review is to describe clinical evaluation tools used in the last decade to assess motor functioning and musculoskeletal abnormalities of patients with RTT.

Methods

This systematic review of literature was carried out based on the principle described in the PRISMA Statement[31,32] on articles published between January 2009 and February 2019. No review protocol exists. A bibliographic study was conducted by consulting PubMed, Web of Science, and Scopus databases. The keywords used for this search were: "Rett syndrome" associated through the Boolean operator "AND" to "assessment", "evaluation", "measure", "questionnaire", "gross motor function", "physical activity", "deformity", "muscle tone", and "gait" associated to each other with the operator "OR". "Mice" and "rat" words were excluded from the search through "NOT" Boolean operator, also these words were associated using the "OR" operator. All "OR" operations were run first (included in parenthesis). Exact keywords used to search each database are shown in Table 1. A filter for selected publishing timespan was used for all databases. Further relevant clinical studies were found in the bibliography of the already retrieved articles. Last search was conducted in March 2019. Included studies selection followed four steps: i) after first online databases search, obtained results were checked to remove duplicates; ii) remaining paper titles were analyzed to identify possible pertinent articles; iii) abstract of the selected articles were read to identify research that was full-text read; iv) selected full-text articles were read and inclusion/exclusion criteria were applied to identify included papers.

Inclusion Criteria

This review includes articles published in English between January 2009 and February 2019 as full-papers in peer-reviewed journals that involved at least one participant with genetic diagnosis of classical Rett syndrome (MeCP2 mutation) evaluated using specific or a-specific evaluation tools that measured activity, activity limitation (e.g. muscle tone alteration, involuntary movements), mobility, gross motor function, or lower limb musculoskeletal abnormalities. To be included, the evaluation tools had to be: constructed specifically to evaluate at least one of these categories or having a specific subscale to evaluate at least one of these categories or presenting at least two items to assess lower limb musculoskeletal abnormalities or activity limitations or at least three items to assess gross motor function.

Exclusion Criteria

Articles not written in English, those published before 2009 or after February 2019 and those that did not include participants with genetic diagnosis of classical Rett syndrome were excluded. Investigations carried out with tools individualized for each child using semi-structured interviews were also excluded. No exclusion criteria were applied for the study design to allow identification of all the evaluation tools including those used in case report studies. Book chapters, article commentaries, conference abstracts or posters and articles not included in selected database were excluded from this review.

Table 1. Keywords used for databases search and number of articles obtained from each search.

Database	Key-words	No of articles found
Pub Med	(Rett syndrome AND (assessment OR evaluation OR measure OR questionnaire OR gross motor function OR physical activity OR deformity OR muscle tone OR gait) NOT (Mice OR rat))	432
Web of Science	ALL = ((Rett syndrome) AND (assessment OR evaluation OR measure OR questionnaire OR gross motor function OR physical activity OR deformity OR muscle tone OR gait) NOT (Mice OR rat))	368
Scopus	TITLE-ABS-KEY ("rett syndrome") AND (ALL ("assessment" OR "evaluation" OR "measure" OR "questionnaire" OR "gross motor function" OR "physical activity" OR "deformity" OR "muscle tone" OR "gait")) AND NOT ("mice" OR "rat")	520
Total number of articles found:		1320

Data Extraction

Information regarding study aim, participant characteristics, description of tools used, and relevant outcome obtained with motor evaluation tools were extracted for each included article. When available for RTT population, information regarding psychometric characteristics of the tools were also collected including reliability, validity, responsiveness, feasibility and clinical utility.

Results

From the first electronic databases search, 1320 articles were identified (432 from PubMed, 368 from Web of Science and 520 from Scopus). After duplicates were removed, 880 articles remained. Title reading led to the removal of 762 manuscripts. Abstracts of the remaining 118 were read. Abstract reading evidenced 82 papers to be full-text read. Of those full-text read, 34 satisfied the inclusion and exclusion criteria for this review. Article selection procedure is represented as a flow chart in Figure 1. Data extracted from the included manuscripts are presented in Table 2.

Among the 34 included articles, 21 different motor evaluation tools were identified. Two of these were adaptations from other tools previously described in the literature. A summary of the evaluation tools identified is reported in Table 3.

Among the identified evaluation tools, 12 were built or adapted specifically to assess RTT subjects, eight were created for a general population or other disease/disorder and three were electronic devices. Four tools were RTT clinical severity scales which included gross motor items. Three scales were RTT-specific gross motor evaluation tools.[9,55,69,75] One tool was used to score adaptive behavior including mobility domain.[65] Three assessments were nonspecific functional status evaluations.[66,70,73] The three electronic devices were all inertial sensors (StepWatch Activity Monitor™ – Modus Health, LLC, Washington, DC; ActivPAL™ – PAL Technologies, Glasgow, UK; Actigraph™ GT3X – ActiGraph, Pensacola, FL, USA) and together with one individualized tool[49] were aimed to measure daily physical activity. Two assessments were used to evaluate muscular abnormalities: one is RTT specific and measures muscular rigidity[19], the other is usually used with cerebral palsy and scores muscle spastic hyper tone.[68] One scale is an RTT nonspecific gross motor and aid tolerance scale.[71] Three evaluation tools are functional mobility

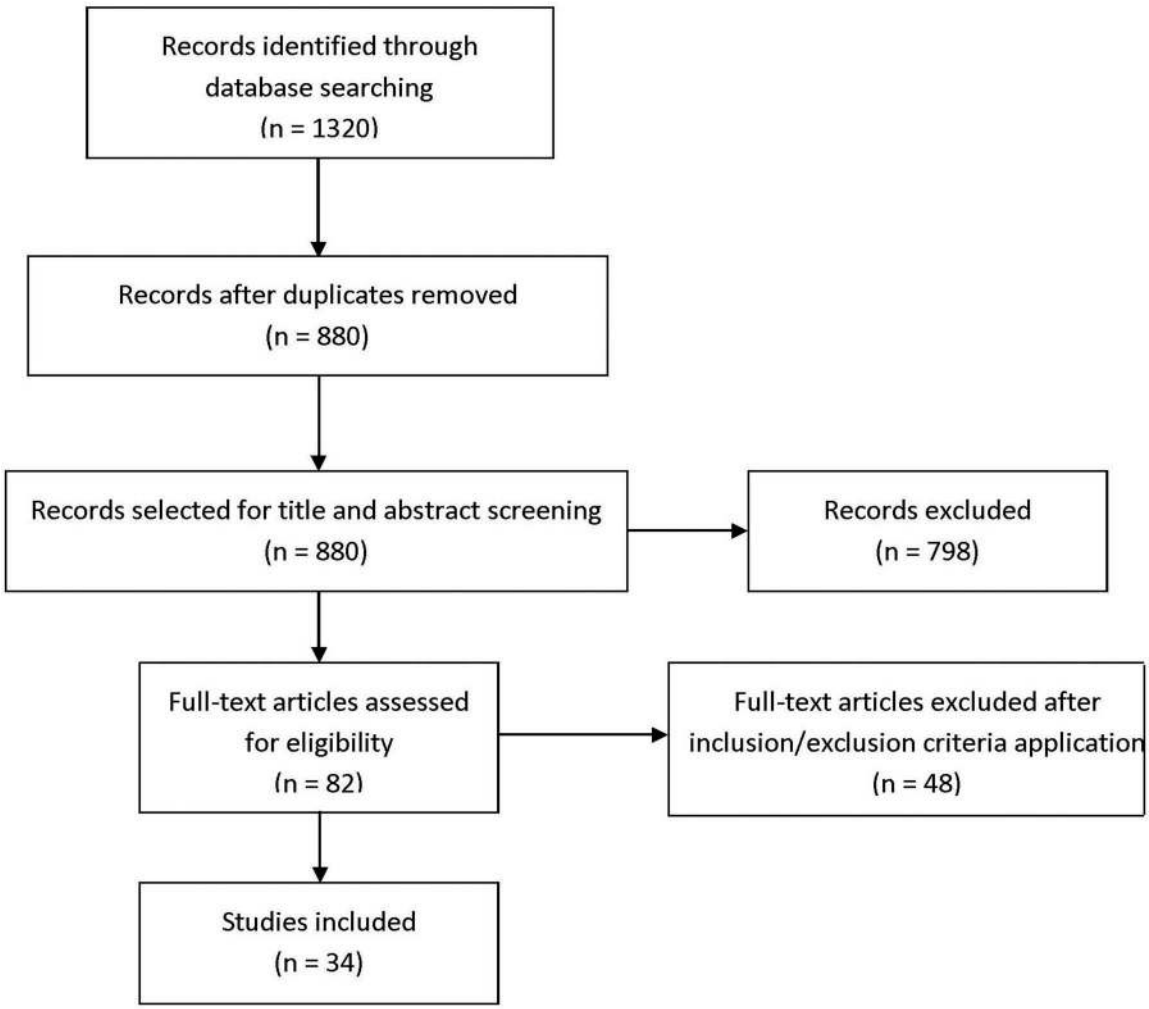

Figure 1. PRISMA diagram for study selection.

Table 2. Data extracted from the included articles.

Reference	Aim	Participants	Used tools
33	First aim: to examine the profiles of anxious behavior in a sample of girls with RTT, with a focus on further delineating the range of manifestations and their relationship with other abnormal behaviors and clinically relevant parameters. Second aim: to identify the instrument with the best psychometric properties in this population.	74 girls, ages ranging from 2 to 11 years (M = 5.35; SD = 2.36), with typical RTT	Rett Syndrome Behavior Questionnaire (RSBQ); Anxiety Depression and Mood Scale (ADAMS); Aberrant Behavior Checklist-Community (ABC-C); Clinical Severity Scale (CSS); Vineland Adaptive Behavior Scales-II (Vineland-II); Child Health Questionnaire (CHQ).
34	To compare severity and age of onset of symptoms in those with and without a large deletion.	974 individuals including 51 with a large deletion and ages ranging from 1 year 4 months to 49 years (median 9 years).	Kerr, Percy and Pineda Scales
35	To explore foot deformity prevalence in a Rett population and relationship with standing and walking abilities	67 subjects with Rett, age range: 2 – more than 50 yr	Rett Syndrome Gross Motor Scale; ad hoc questionnaire (assessing PROM, foot deformities, weight bearing, type of orthosis)
36	To add evidence on age-related clinical and behavioral change into adulthood for individuals with Rett	91 subjects with Rett, 69 with typical Rett; ages ranged from 4 to 47 years with a mean of 20.5 years	Vineland Adaptive Behavior Scale – Survey Form (VABS); Rett Syndrome Behavioral Questionnaire (RSBQ); Health Questionnaire; The Activity Questionnaire (TAQ); Mood, Interest and Pleasure Questionnaire Short Form (MIPQ-S); Repetitive Behavior Questionnaire (RBQ); Challenging Behavior Questionnaire (CBQ).
37	To obtain a UK national RTT sample principally to investigate the associated behavioral phenotype in comparison to a well-chosen contrast group and its relationship to parental well-being: focuses on abilities and health in relation to diagnostic, clinical, and genetic mutation categories.	91 subjects with Rett, 69 with typical Rett; ages ranged from 4 to 47 years with a mean of 20.5 years	Simplified severity score; Health questionnaire; Non-communicating children's pain checklist (NCCPC-R); Gastro-esophageal distress questionnaire (GDQ); Vineland adaptive behavior scale – survey form (VABS)
38	To investigate relationships between hand function and genotype and aspects of phenotype in Rett syndrome.	144 females with a mean age of 14 years 10 months (SD 7 y 10 mo; range 2–31 y 10 mo)	14 items from Kerr et al., 2001 score; WeeFIM.
39	To establish the capacity of StepWatch to measure walking activity in Rett; to describe walking activity over whole-day periods and explore relationships with age and gross motor skills	12 subjects with Rett, mean age: 12.9 ± 8.0 yr, range: 2-27 yr	StepWatch Activity Monitor (SAM); RSGMS
40	To investigate the capacity of three accelerometer-type devices to measure walking activity in Rett syndrome.	26 subjects with Rett, mean age: 18 ± 8 y	RSGMS; Actigraph; ActivPAL: StepWatch Activity Monitor (SAM).
41	To explore and analyze the proportion of waking hours spent in walking-based physical activity, across a range of cadences, and the proportion of waking hours spent in sedentary time in those with Rett syndrome. Second aim: examined the influences of age, walking ability, scoliosis, and seizure frequency on the average total daily step count and sedentary time in this population.	64 subjects with Rett, mean age: 17 y 7 mo ± 9 y, range: 3y 6 mo to 38 y	StepWatch Activity Monitor
42	To investigate the effects of environmental enrichment on gross motor skills and blood BDNF levels in girls with Rett syndrome	12 subjects with Rett, mean age: 3 ± 1.1 y, range: 1.5–5.2 y	RSGMS; BDNF blood level; Sleep Disturbance Scale for Children – DIMS subscale; Rett Syndrome Behavior Questionnaire – Mood subscale; BMI.
9	First aim: to replicate principal components analysis of the RSGMS using current larger dataset and to assess relationships of motor scores with genotype and age. Second aim: to investigate the consistency of observed and parent reported ratings and to describe the test-retest and within-subject reliability of the RSGMS.	255 subjects with Rett, age range: from <8 y to >19 y	RSGMS

(*Continued*)

Table 2. (Continued).

Reference	Aim	Participants	Used tools
43	To use the prospectively collected parent-reported data in this database to examine effects of scoliosis surgery on functional outcomes and to compare these effects with changes for a similar period in girls/women who also had scoliosis but did not have surgery.	102 subjects with Rett; 86 without spinal surgery (mean age at posttest: 13.1 range: 4.3–23.9); 16 with spinal surgery (mean age at posttest: 15.2 range: 14.1–16.4).	Modified parent-report WeeFIM
44	To correlate disease-causing genetic mutations to the variety and intensity of the detailed symptomatic parameters assessed by RARS and to provide insights into the effect of MECP2 mutations on RTT phenotype.	114 subjects with Rett, ages ranged from 2 to 36 years (mean = 14.10 years, SD = 9.75)	Rett Assessment Rating Scale (RARS)
45	To investigate the course of gross motor function in girls/women with Rett syndrome over a 3- to 4-year period and investigate the nature of any changes in relation to age and genotype.	70 subjects with Rett mean age at T0: 13.7 y	Fyfe video-based evaluation tool
46	To investigate relationships between genotype and specific clinical data collected by the same experienced physician in a well-documented RTT cohort	137 subjects with Rett, 80% (n: 109) were categorized as classic RTT and 20% (n: 28) as variant RTT; mean age: 14.9 y, range: 2–49, SD: 10.7	International Scoring System (ISS) (Adapted from Kerr et al., 2001)
19	To report a cross-sectional and prospective evaluation of the appearance, anatomical distribution, and progression of increased muscle tone and rigidity in a cohort of RTT children, youths, and adults assessed and followed at a neurology clinic dedicated to this disorder.	51 subjects with Rett age range: 2 y5mm-54 y	Rett Syndrome Rigidity Distribution score (RTTRD)
47	To evaluate Anticipatory Postural Adjustments (APA) during gait initiation in RTT	18 ambulant subjects with Rett mean age: 9 ± 3 y	Rett Assessment Rating Scale (RARS); Optoelectronic system BTS
48	To examine the potential of robotic technology to evaluate rigidity in persons with Rett Syndrome to determine whether the participants would tolerate robotic evaluation and to compare the results with young healthy adults.	3 subjects with Rett age: 15 y, 18 y, and 23 y.	Modified Ashworth Scale (MAS); InMotion Arm and hand (MIT-Manus); InMotion Wrist; InMotion Ankle.
49	To investigate the validity of using a Bouchard activity record (BAR) in individuals with Rett syndrome to measure physical activity, as compared with pragmatic criterion standard measures of walking status and step counts recorded using the StepWatch activity monitor (SAM).	43 ambulant subjects with Rett mean age: 21 ± 9 y	Modified Bouchard Activity Record (mBAR); StepWatch Activity Monitor (SAM)
50	To evaluate if conductive environment programme based on the general conditions for learning would improve functional skills of girls with RTT.	3 girls with Rett age: 3 y, 4 y, and 5 y.	Rett Functional Evaluation Scale; Rett Syndrome Gross Motor Scale (RSGMS)
51	To highlight the clinical manifestations of RTT; to evaluate the genotype–phenotype relationship; and to assess the possible relationship between the severity score, clinical manifestations, and MECP2 gene mutations.	15 subjects with RTT, age range: 9 months to 5 years.	International Scoring System (ISS) Adapted from Kerr et al., 2001)
8	To characterize and identify areas of greater functional abilities and verify functional differences between persons at stages III and IV of RTT.	38 subjects in stage III of Rett mean age: 9.14 ± 5.84; range: 2.2–26.4 y. 22 subjects in stage IV of Rett mean age: 12.45 ± 6.17 y; range: 5.3–26.9 y	Pediatric Evaluation of Disability Inventory (PEDI)
52	To provide information on the relationship between specific mutations in the MECP2 gene and function based on skill assessments in addition to parent report and neurologic examination.	96 subjects with Rett, mean age: 6.2 y SD: 0.8 y	The Functional Independence Measure for Children (WeeFIM); Physical Abilities and Mobility Scale (PAMS); Upper Extremity Measurement Scale (UEMS)
53	To describe the clinical and autonomic features of RTT girls who attend the Tuscany Rett Center, to obtain more information on the correlation between genotype and phenotype.	151 subjects with RTT, 2 males, 98 classical, 19 Zappella RTT (Z-RTT), 13 Hanefeld variant, 1 congenital variant, 20 Atypical RTT not otherwise specified (ARTT-NOS). mean age: 12 y, range: 1-49 y, median: 10 y	Pini Bonuccelli Zappella scale: PBZ; International Scoring System (ISS) Adapted from Kerr et al., 2001)
54	To describe the prevalence of scoliosis, classify spinal deformity, and evaluate the association between disability and scoliosis in patients with Rett syndrome.	29 subjects with RTT, mean age 14 years 8 months, range 4 y 10 mo–33 y	Barthel Index for assessment of disability
55	To assess whether clinicians' and parents' scores agreed, and the strength of the correlation. A secondary objective was to assess the association of motor impairment with specific genetic mutations, and to evaluate the impact of severity of scoliosis on (loco-)motor function.	60 subjects with Rett mean age: 12 y 5 mo ± 8y 9 mo; range: 3–40 y	Rett Syndrome Motor Evaluation Scale (RESMES); Pain Assessment in Advanced Dementia scale; Rett Assessment Rating Scale (RARS); Modified Ashworth Scale (MAS); Scale of evaluation of purposeful hand function; Scale of assessment of scoliosis.

(*Continued*)

Table 2. (Continued).

Reference	Aim	Participants	Used tools
56	To describe what to expect from aging women with RTT regarding some of the basic functional abilities that are used in daily activities and that could have an impact on quality of life in these women.	27 subjects with Rett mean age: 40.7 y median age: 43 y range: 30-60 y	Clinical Severity Score (CSS); WeeFIM (Self-care subscale); Hoffer ambulation scale (HAS) modified by Vodel et al. 2007; Level of purposeful hand function; RSGMS
57	To establish so-called disorder profiles or subgroups in RTT based on this extended clinical follow-up and in relation to the type and localization of the MECP2 mutation.	103 subjects with RTT: mean age: 16.6 y, range: 2-60 y,	International Scoring System (ISS) Adapted from Kerr et al., 2001); Simplified ISS
58	To describe patterns of sedentary time and daily steps in girls/women with RTT; to identify associations between individual and environmental characteristics with sedentary time.	48 subjects with Rett, median age: 22.0 (IQR:14.3–36.5); age range: 5.5–60.5 y	ActivPAL; StepWatch Activity Monitor (SAM); Clinical Severity Score (CSS); RSGMS
12	To modify two existing measures of walking capacity (2MWT) and performance (FMS) to enable their use in RTT and (2) to examine the concurrent validity and test–retest reliability of these measures in girls and women with RTT.	42 subjects with RTT, age range = 2.4–60.9 y; median = 18.4 y	Modified 2-min walk test (2MWT); functional mobility scale-Rett syndrome (FMS-RS); Clinical severity Scale (CSS); Rett syndrome gross motor scale (RSGMS); Pediatric evaluation of disability inventory (PEDI).
59	Aim one: to examine the accuracy of ActivPAL to measure sedentary time, standing and walking. Aim two: to compare sedentary time recorded on the modified Bouchard activity record and sedentary time measured using ActivPAL.	26 subjects with Rett, median age: 16.0, range: 9.4–20.6 for Aim one. 11 subjects with Rett, median age: 14.5, range: 11.5–25.6 for Aim two.	ActivPAL; modified Bouchard Activity Record (mBAR)
60	To determine the prevalence of hip displacement and spinal deformity in a clinic population of females with Rett syndrome to define implications for screening and management.	31 subjects with Rett, mean age: 15 y 6 m (SD 5 y 4 m)	Functional Mobility Scale; RX
61	To assess factors that could influence use of equipment and respite services among Australian families caring for a girl/woman with Rett syndrome and examined relationships between use of these resources and later caregiver health.	170 subjects with Rett, mean age: 13.4 ± 6.0 y; range: 2–28 y	Modified Kerr scale (as in Colvin et al., 2003); The Rett syndrome behavior questionnaire (RSBQ); Accessibility/Remoteness Index of Australia (ARIA+); Socio-Economic Indexes for Area (SEIFA); Australian and New Zealand Standard Classification of Occupations (ANZSCO); SF-121 Health Survey.
62	To delineate if and how neurological and neurophysiological impairment reflects behavioral and neuropsychological functions, to identify prognostic factors that could be important in the clinical management of girls with RTT	18 subjects with Rett, Mean age: 13.7 y; range: 7 – 21 y	Vineland Adaptive Behavior Scales; Rett Assessment Rating Scale (RARS);

tests: one created for a general population[74] and two specifically adapted to be used with persons with RTT.[12] The identified instruments are analyzed below divided into the aforementioned categories.

RTT-Specific Gross Motor Evaluation Tools

Rett Syndrome Gross Motor Scale (RSCMS)

This scale was proposed by an Australian team who adapted the Gross Motor Function Measure[76,77] and includes additional items to produce an assessment suitable for individuals with RTT.[75] Validation of this scale was carried out on a sample of 255 individuals divided into four age groups (<8 y, 8 < 13 y, 13 < 19 y, and ≥19 y, respectively). RSGMS showed an excellent repeatability of clinical assessment, using Cohen's Kappa statistic. Kappa values indicated moderate to good agreement with values ranging from 0.47 for sit to stand to 0.75 for running.

The RSGMS includes 15 items which coded the highest ability of sitting on the floor, sitting on a chair with and without a back, standing for three, 10 and 20 s, walking 10 steps, side stepping, turning 180°, walking along a slope, stepping over an obstacle, running, transfers from sitting to standing, standing up from the floor, and bending down to touch or pick up an object on the floor and returning to standing. Scores were given to each item based on assistance needed to perform the task on a 4-point discrete scale from 0 (no assistance needed) to 3 (maximal assistance requested or unable to perform the task).[17,75] Using principal component analysis, this scale was divided into three subscales named sitting subscale (three items), standing and walking subscale (nine items) and challenge subscale (three items).

As above stated, this scale showed strong internal consistency both for the total scale (Cronbach's alpha coefficient = 0.96) and for the three subscales (Cronbach's alpha coefficients: sitting subscale = 0.83; standing and walking subscale = 0.97; challenge subscale = 0.85) and excellent repeatability (Intraclass

Table 3. Characteristics of the evaluation tools identified in the included articles.

Tool name	Reference/URL to found	Tool type	Motor items/subscales characteristics
Kerr scale (or International Scoring System – ISS)	63	20-item RTT specific severity scale	One item on muscle tone; one item on generic joint contractures; one item on walking ability; one item on presence of involuntary movements; one item on lower extremities peripheral circulation. Score on 3-points scale from 0 (normal) to 2
Percy scale	64	15-item RTT specific severity scale	One item on sitting skill acquisition; one item on crawling skill acquisition; one item on walking ability and acquisition; one item on lower extremities peripheral circulation. Different scoring system for each item. Lower score corresponds to lower severity.
RSGMS	9	15-item RTT specific gross motor scale	3-item sitting subscale (sitting on the floor, on a chair and on a stool for 10 sec respectively); 9-item standing and walking subscale (sit to stand, standing for 3, 10 and 20 sec, turns, walks on a slope, step over obstacle, stands up from the floor, bending to touch the floor and return); 3-item challenge subscale (walks 10 steps, side steps, runs). Score on 4-points scale from 0 (maximal assistance needed) to 3 (no assistance needed).
VABS – survey form	65	297-item non-RTT specific adaptive behavior survey	40 age-related-item gross motor subscale; 36-age-related-item fine motor subscale. Score on 3-points scale from 0 (Never) to 2 (often).
The Functional Independence Measure for Children (WeeFIM)	66	18-item non-RTT specific functional scale	Includes a mobility domain with 5 items (chair, toilet, and tub transfers, locomotion, and stairs). Score on a 7-points scale from 1 (need for total assistance) and 7 (complete independence).
StepWatch Activity Monitor™ (SAM)	Modus Health, LLC, Washington, DC – https://modushealth.com	Single sensor device – Dual-axis accelerometer	Measures number of steps taken also at slow pace and time spent without walking activity.
ActivPAL™	PAL Technologies, Glasgow, UK – http://www.palt.com	Dual sensor device – Uni-axial accelerometer, inclinometer.	Measures number of steps taken, and the time spent in supine and sitting from the time in standing and walking.
Actigraph™ GT3X	ActiGraph, Pensacola, FL, USA – https://www.actigraphcorp.com	Dual sensor device – tri-axial accelerometer, inclinometer.	Measures activity intensity and number of steps taken.
RARS	67	31-item RTT specific severity scale	Includes a motor domain with 4 items: body (ability to stand and walk); hands, scoliosis, feet (lower extremities peripheral circulation, growth and deformities). Plus one item on muscular tension. Score on a 7-points scale from 1 (need for total assistance) and 7 (complete independence). Score on a 4-points scale, from 1 (within normal limits) to 4 (severe abnormality), intermediate ratings (+0,5) are also possible.
Rett Syndrome Rigidity Distribution score (RTTRD)	19	15-item RTT specific muscular rigidity score	15-muscle groups rigidity evaluation. Score from 0 (no rigidity) to 1 (presence of rigidity) for each muscle group.
MAS	68	non-RTT specific muscular spasticity score	Grades muscle spasticity in terms of response of muscle tone to passive stretching. Score on a 5-points scale from 0 (normal muscle tone) to 4 (limb rigid in flexion or extension). Score 1+ could be assigned in the modified version.
mBAR	49	RTT specific proxy-reported diary card for physical activity	Scores physical activity in each 15-minute period over a whole day. Score from 1 (lying) to 5 (walking at a vigorous intensity).
Rett Functional Evaluation Scale	Precise instruction and materials unavailable in the referred articles –69	31-item RTT specific gross motor scale	Measures the ability of participants to knee walk and stand, to get up to a standing position, to walk at different speeds, and to go up and down stairs and slopes. Score on 12 levels of performance for each item recording the time it takes to complete a task. Grades gross motor function from 0 to 372 points.
PEDI	70	237-item non-RTT specific functional status assessment	Measures functional status in children aged between 6 and 90 months. Includes a mobility subscale with: 59 items for functional skills (score between 0 – Unable, or limited in capability; and 1 – Capable of performing item in most situations); 7 items for caregiver assistance (score between 0 = Total assistance and 5 = Independent); 7 items for resolution pattern modifications (structured note between "N" = No modifications and "E" = Extensive Modification).
PAMS	71	20-item non-RTT specific movements and positioning scale	Evaluates orthosis and aids tolerance and gross motor functioning. Score for each item on 5-point scale (from 1 = unable to complete to 5 = able to complete in a normal manner).
PBZ	72	26-item RTT specific severity scale	Includes a motor area subscale with nine items (facial mimic; eyes gaze; praxic actions; hand stereotypies; walking; sitting; muscles tone; trophism; movement disorders) and two items for the ability to climb and descend stairs. Score on 5-points scale (from 0 = normal to 4 = very severe).

(*Continued*)

Table 3. (Continued).

Tool name	Reference/URL to found	Tool type	Motor items/subscales characteristics
Barthel Index	73	10-item non-RTT specific functional independence index	One item on bed to chair transfer (score on four levels from 0 = Unable to 15 = Independent); one item on mobility on level surface (score on four levels from 0 = Unable or <50 yd to 15 = Independent or with aids); one item on ability to perform stairs (score on three levels from 0 = Unable to 10 = Independent). Each scoring level is worth five points.
RESMES	55	25-item RTT specific gross motor scale	six dimensions: standing; sitting; transitions; walking; running; and walking up/down stairs. Scored on 5- or 3-points scale (depend on selected item) from 0 (unable to perform the task) a 4 or 2 (independent) an ordinal scale (0–4 for 16 items; 0–2 for nine items).
2MWT	12	RTT-adapted Functional walking test	The test assesses how far (meters) a person can walk in 2 minutes.
FMS-RS	12	RTT-adapted Functional mobility test	Assesses walking performance over three distances: 5 m, 50 m, and 500 m corresponding to home ambulation, day center ambulation and community ambulation, respectively. Score on a 5-point scale from 0 (unable to walk) to 4 (independent) based on the level of assistance needed to walk the given distance.
FMS	74	non-RTT specific Functional mobility test	Assesses walking performance over three distances: 5 m, 50 m, and 500 m. Each distance receives a score on 6-points scale from 1 (uses a wheelchair) to 6 (independent on all surface) based on the level of assistance needed to walk the given path.

Correlation Coefficient for total score = 0.99, 95% CI 0.93–0.98). The minimal detectable change for this scale was found to be four points on the total score.[9] The RSGMS was used in several cross-sectional and longitudinal studies which described RTT gross motor functioning also related to genotype and subject's age[12,58,78] but was implemented in few studies aimed to evaluate the efficacy of rehabilitation training.[50] Finally, this scale was used in a study aimed to examine the effects of environmental enrichment on gross motor skill in a group of 12 children with RTT (mean age: 3.0 y, SD 1.1 y; range: 1.5–5.2 y).[42] The RSGMS is available in the literature attached to the referred article.[9]

Rett Syndrome Motor Evaluation Scale (RESMES)

This recently published scale was created by an Italian team on the basis of the capacity construct of the International Classification of Functioning, Disability, and Health[42] to address functional motor abilities not included in the RSGMS (e.g. postural transitions, climbing or descending stairs).[79] This tool is a 25-item ordinal scale examining (loco-)motor function across six sections: standing, sitting, transitions, walking, running, walking up/downstairs. Sixteen items are rated on a 0–4 discrete scale, where 0 indicates null or very mild impairment and 4 severe impairment for a total maximum score of 82 points. Nine items related to walking abilities were rated on a 0–2 discrete scale, 0 indicates that task could be always completed by the subject and 2 indicates that the task could not be 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. The patient classification (i.e. motor dysfunction severity) is due to score classes, as follows: stanine values of 1 to 2, 3 to 4, 5 to 6, and 7 to 9 correspond, respectively, to a level of minimal (or null), mild, moderate, and severe impairment, respectively.

Moreover, RESMES was also designed to be proxy performed by parents. Comparison between total score obtained by parents and clinicians revealed a high correlation and no statistical difference. All items of the scale showed significative correlation between parents' and clinicians' evaluations. However, six items showed statistical difference between proxy and professionals' evaluations where parents tended to report lower scores. Also, low to moderate correlation of RESMES with Rett Assessment Rating Scale (RARS), Modified Ashworth Scale (MAS), severity of scoliosis, and purposeful hands use were described.[55]

This scale was recently validated on a sample of 60 females with RTT (mean age: 12 y 5 mo, SD 8 y 9mo; range: 3–40 y) showing optimal inter-rater agreement among clinicians (s* statistic values always >0.70) and strong internal consistence (split-half reliability coefficient = 0.96 SD 0.18; Cronbach alpha coefficient for the entire scale = 0.95 CI 0.93–0.97).[80] In literature, the RESMES was administered in two articles to describe the psychometric properties of the scale[80] and to present the comparison between the assessments conducted by clinicians and parents and the correlations with aforementioned clinical assessments.[55] So far, RESMES has not been used in clinical studies but shows the potential to be sensitive enough to be used in a rehabilitative setting. The RESMES is available in the literature attached to the referred article.[55,80] Overall, it is a new, valid and reliable scale that can be used in clinical practice when assessing motor function of subjects with RTT.

Rett Functional Evaluation Scale (RFES)

This is a 30-item scale that measures the ability of participants to knee walk and knee stand, to get up to a standing position, to walk at different speeds, and to go up and down stairs and slopes. The measurement tool considers 12 levels of performance for each item recording the time it takes to complete a task, thus providing a consistent grading from 0 to 372 points using seconds in time and meters in distance. The RFES was validated by a committee of three independent experts in child with developmental and cognitive impairment. It has been found to have high inter-rater reliability and to be sensitive to changes of functional abilities in four girls with RTT aged between 8.5 and 11 years (mean age: 10 y) who participated in

a 2-month treadmill program. This scale was used in two case studies to measure the effects of rehabilitative intervention.[50,69] This scale should be requested to the authors privately as it is not available attached to the referred articles.

Daily Physical Activity Measurement Tools

StepWatch Activity Monitor™ (SAM)

This is a single sensor device with a dual-axis accelerometer that measures the number of steps taken by the user. It is attached around the ankle close to the lateral malleolus with an elastic and Velcro strap. SAM contains adjustable filters that enable steps to be counted in a range of gait styles including slow pace and short quick steps. Data on physical activity derived from the software include the count of steps taken and the percentage of time in sedentary behavior, defined as an absence of steps. One study that included 12 females with Rett syndrome aged between 2 and 27 found no differences between number of steps measured with SAM and through video recording.[39] SAM was used to measure the amount of daily activity and sedentary time in RTT. In a study which included 64 female with RTT (mean age: 17 y 7 mo, SD 9 y; range: 3y 6 mo to 38 y) the authors used SAM to demonstrate that adults with RTT engaged in less walking-based physical activity than children younger than 13 years and both adolescents and adults were more sedentary than children.[41]

Six studies investigated test–retest reliability of SAM in participants with different motor disorder: stroke, diabetic peripheral neuropathy with or without amputations, spinal cord injury, neurological disorders, and control participants. The studies measured mean steps/day and compared 2 separate time periods within 3 weeks although one study did not report statistics. The intraclass correlation coefficients for mean steps/day ranged from 0.86 to 0.99 indicated an excellent test–retest reliability. SAM is for sale at the producer.

ActivPAL™

This is a dual sensor device with a uniaxial accelerometer and inclinometer that is attached to the thigh using an adhesive pad. Detecting the thigh inclination and limb movement, ActivPAL™ provides information regarding the number of steps taken and the time spent in a supine and/or sitting position or in standing and walking activity.[39] This device was found to be highly accurate in estimating sedentary time through thigh position analysis, but showed poor validity in measuring steps in RTT.[39,58]

Actigraph™ GT3X

The Actigraph™ GT3X is a device with a triaxial accelerometer and an inclinometer that is attached to the waist using an elasticized belt measuring activity counts, vector magnitude and steps taken. It was created for a general population and as such its filters are not suitable to measure steps and activity in subjects with RTT as it shows a high variation in the step count compared with those counted through video recording.[40] The reliability and validity of the ActiGraph GT3X accelerometer show an excellent reliability and validity to measure physical activity during walking and can be appropriate in rehabilitation research and clinical practice.

Modified Bouchard Activity Record (mBAR)

This is a whole-day diary card on which, for every 15-min period of the day, a number can be assigned to the level of intensity of physical activity performed by the subject in the analyzed period. The original version of the Bouchard Activity Record (BAR) was proposed to be used in the general population and considered nine levels of physical activity intensity.[41] In the modified version, the observation is carried out by proxy (e.g. by the caregivers) and the number of levels is reduced from nine to five to make it more relevant to the severe disability associated with Rett syndrome. The modified scale comprises the following items: 'lying'; 'sitting for mealtime or other activities'; 'light activities in standing', 'walking at a slow intensity' (defined as walking gently, such as when walking around the house), and 'walking at a vigorous intensity'.[49] A validation study of mBAR showed a correlation with the number of steps taken during the day for the subjects who can walk independently. Moreover, in another study, the summation of the period spent in a lying or sitting position was very representative of the amount of sedentary time measured with the ActivePAL™ electronic device for 11 female subjects with RTT (median age: 14.5 y; range: 11.5–25.6 y).[59] A study examined the relationships between the mBAR and two pragmatic criterion standard objective measures: the participant's walking status and step counts measured using the previously validated SAM. The results indicated a good reliability for the use of mBAR in RTT population. mBAR is available in the literature attached to the referred article.[49]

Mobility Items of RTT-specific Severity Scale

Kerr Scale (also Named International Scoring System – ISS)

This is a 20-item scale to assess the severity of the pathology of subjects with RTT giving each item a score between 0 (normal) and 2 (severe abnormality). Among the 20 items, the ISS offers the possibility to give a score to subject's muscle tone, joint contracture (only one score for the entire body, no discrimination between body joints), walking ability, the presence of involuntary movements (in addition to hand stereotypes), circulation in the extremities and trophism.[63] Kerr scale was largely used in both clinical practice and research to provide a general clinical picture of subjects with RTT across several domains. In the research field, this scale was mainly used to investigate the correlation of the severity of the pathology manifestations with genotype.[34,46,51,53,57,81,82] One study investigates the relation between clinical severity and hand function level in a group of 144 female individuals with RTT (mean age: 14 y 10 mo, SD 7 y; 10 mo; range 2 y to 31 y 10 mo).[38] Another research uses the Kerr scale to explore the relation between the severity of the disease and socio-economic condition of 170 families with daughters with RTT (mean age: 13.4 y, SD 6.0 y; range: 2–28 y).[61]

Percy Scale

The Percy scale evaluates the severity of the clinical picture of subjects with RTT across 15 items. It includes three items of

gross motor skills scored on different discrete scales based on the age of ability acquisition. The sitting item scores the age of acquisition of the ability to sit between 0 (acquired by 8 months) and 2 (never acquired). A score of 1+ can be given if the ability has been lost. The ability to crawl/creep can be scored between 0 (acquired by 12 months) and 3 (never acquired). Ambulation acquisition can be scored between 0 (acquired by 18 months) and 5 (never acquired). A score of 2 + or 1+ can be applied if the ability was lost at 30 months or after, respectively. Moreover, also the Percy scale has an item on autonomic dysfunction which scores the feet or hand color and temperature conditions between 0 (normal) and 3 (severe cold/blue/sweaty feet and/or hands). A score of 1+ can be assigned if the problem was present but has been resolved.[34,64] Percy scale was mainly used in literature to investigate the correlation between the clinical severity of RTT with genotype and age[25,27,83], but also with clinical features of the pathology such as oxidative stress markers.[84] One retrospective study used only the item of this scale related to crawling ability as a part of global evaluation to investigate the correlation between the RTT genotype and early development of the participants.[85] Percy scale is available in the literature[64] and was frequently used in association with Kerr scale.

Rett Assessment Rating Scale (RARS)

RARS is a 31-item RTT-specific severity scale. Each item concerns a specific phenotypic characteristic and can be rated on a 7-point ordinal scale as follows: 1 = within normal limits; 2 = infrequent or low abnormality; 3 = frequent or medium-high abnormality; 4 = strong abnormality. Intermediate rates can be endorsed adding 0.5 points to the selected score (the maximum applicable score remains 4). The "Body" item of this scale scores the subject's ability to stand and walk. Also, RARS includes an item to give a score to conditions of the feet with attention to both peripheral circulation and musculoskeletal deformities. Lastly, this scale includes an item on the presence and entity of muscular tension.[44,62,67] The RARS was established by a standardization procedure, involving a sample of 220 patients with RS, proving that the instrument is statistically valid and reliable. More precisely, normal distribution analyses of the scores were computed, and the mean scores of the scale were similar to the median and the mode. Skewness and kurtosis values, calculated for the distribution of the Total score, were 0.110 and 0.352, respectively. The distribution was found to be normal. Cronbach alpha was used to determine the internal consistency. Cronbach's alpha of the total scale was 0.912, and the internal consistency of the subscales was high (0.811–0.934).[62] This scale was presented in the literature to investigate the correlation between clinical severity with neurophysiological and motor evaluations. One study found a moderate correlation between RARS score and EEG abnormalities (r = 0.64, $p < .01$) in a group of 18 girls with RTT (mean age: 13.7 y; range: 7–21 y).[62] One other study investigates the correlation of RARS score with RESMES in a group of 60 females with RTT (mean age: 12 y 5 mo, SD 8 y 9 mo; range: 3–40 y). A moderate correlation between RESMES and total RARS score was found (r = 0.51, $p = .001$) while the score obtained from the motor items of the RARS showed a strong correlation with RESMES (r = 0.82; $p < .001$).[55] RARS is available only in the Italian language.

Pini-Bonuccelli-Zappella Scale (PBZ)

PBZ is an RTT-specific scale comprising 26 items. A score on 5-point discrete scale between 0 (normal) and 4 (very severe) can be applied to each item. This scale contains a motor area subscale which includes two items for walking and sitting abilities, two items on quality of muscle tone and trophism and one item to score presence and entity of dystonia and other movement disorders. Moreover, the PBZ scale contains a subscale on abilities of daily living. In this subscale, two items for the ability of ascending and descending stairs are included.[53,72] This scale was used to outline the clinical and autonomic picture of 151 individuals with typical and atypical RTT (98 with classical RTT – mean age: 12.5 y, SD 10.2 y; 19 with Zappella variant – mean age: 12.5 y, SD 7.9 y; 13 with Hanefeld variant – mean age: 6.1 y, SD 4.8 y; one with congenital variant – age: 2 y; 20 with atypical RTT-not otherwise specified – mean age: 13.5, SD 9.5) .[53] PBZ is available only in the Italian language.

Muscle Condition Evaluation Tools

Ashworth Scale (AS) and Modified Ashworth Scale (MAS)

The AS and its modified version, MAS, are two of the most frequently used clinical methods for estimation of spasticity[86] and hypertonia.[87] Both AS and MAS are performed by passively moving a joint through its range of motions at a standard speed and rating the resistance of stretched muscles on a 6-point discrete scale from 0 (no increase in muscle tone) and 4 (affected part rigid in flexion or extension). Score 1 represents a slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension; score 2 is given when a more marked increase in muscle tone through most of the ROM is observed, but affected part(s) easily moved; the score 3 is assigned if there is a considerable increase in muscle tone or if the passive movement is difficult. A score of 1+ could be assigned if there is a slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM and it represents the difference between AS and MAS. The reliability of MAS has recently been studied in a systematic review and meta-analysis which found satisfactory intra- and inter-rater agreement. The same study also reported that reliability of this measure was better for upper than for lower extremities and that inter-reliability was statistically affected by the characteristics of the study which involves MAS.[88] It is necessary to standardize methods to apply these scales in clinical practice and research.[89] In one study with three females with RTT (ages: 15 y, 18 y, and 23 y, respectively) the MAS was used to evaluate the changes in the subjects' hypertonia before and after the use of robotic tools to assess arm, wrist, and ankle movement.[48] A week correlation between MAS and RESMES scores (r = 0.48, $p < .001$)

was found in a group of 60 females with RTT (mean age: 12 y 5 mo, SD 8 y 9 mo; range: 3–40 y).[55]

Rett Syndrome Rigidity Distribution Score (RTTRD)

This is a recently proposed standardized survey of the anatomical extent of muscle tone rigidity of subjects with RTT. RTTRD scores the presence (score = 1) or absence (score = 0) of rigidity in 15 muscle groups in all four limbs, neck and face (hypomimia serves as a surrogate for muscle rigidity in the face region). This scale was found useful to monitor the evolution of rigidity in 51 females with RTT across age (participants' age range at the first evaluation: 2 y 5 mo to 54 y).[19]

Functional Mobility Test

Functional Mobility Scale (FMS) – Rett Syndrome (FMS-RS)

FMS in its last revision is a score to describe functional mobility in children with cerebral palsy and movement disorders.[74,90] It consists of an observation of the need and the type of aid used by the evaluated subject to walk over three distinct distances: 5, 50, and 500 m. FMS provides a score between 1 (the subject uses a wheelchair to cross the observed distance) and 6 (the subject walks the observed distance independently on any kind of surface) for each distance. FMS was used once with 31 females with RTT (mean age: 15 y 6 mo, SD 5 y 4 mo) as a screening for the functional gross motor abilities of the participants[60] and subsequently adapted to be used specifically with this syndrome.[12] In the version modified for RTT, FMS-RS, the scoring system refers to the level of assistance needed to walk the given distance. A score between 0 (unable) and 4 (independent) is given at each distance. The scoring system has been derived and expanded from the RSGMS. FMS-RS showed strong correlations with showed Pediatric Evaluation of Disability Inventory (PEDI) motor domain RSGMS in a group of 42 girls and women with RTT (median age: 18.4; range: 2.4–60.9 y).[12]

Modified 2-Min Walk Test (2MWT)

2MWT is a functional walking test created as an alternative to the 6-Min Walk Test. This test was frequently used with subjects with stroke and motor and neurological impairments[91–93] and has recently been proposed to be performed with individuals with RTT.[12] In the adapted version of 2MWT for individuals with RTT, the evaluated subject walks back and forth between two cones on a 20-m track for 2 min and the total distance covered is measured. The usual 2MWT protocol was modified to enhance comprehension, motivation, and effort of subjects with RTT. The modified version requires two assessors and one walk assistant. The walk assistant knows the person with RTT well (e.g., parent, caregiver, therapist) and provides the necessary physical support to keep the balance and maintain the highest possible gait speed. 2MWT shows moderate correlation with clinical severity and gross motor abilities in a group of 27 girls and women with RTT (median age: 27.4; Inter Quartile Range: 15.8–39.8 y).[12]

Nonspecific Evaluation Tools

Vineland Adaptive Behavior Scale (VABS) – Survey Form

The VABS – Survey Form[65] is a semi-structured parent interview that provides a general assessment of developmentally adaptive behavior across a variety of domains in children of all ages: Communication skills, Daily Living skills, Socialization skills, and Motor skills. VABScontains 297 items of which 76 are included in the motor domain. Standard scores (mean = 100; SD = 15) and age equivalent scores can be combined to derive an Adaptive Behavior Composite.[94] For each of the four domains and for the Adaptive Behavior Composite, high internal consistency (Communication skills: r = 0.89; Daily Living skills: r = 0.90; Socialization skills: r = 0.86; Motor skills: r = 0.83; Adaptive Behavior Composite: r = 0.94), test–retest reliability (Communication skills: r = 0.86; Daily Living skills: r = 0.86; Socialization skills: r = 0.81; Motor skills: r = 0.81; Adaptive Behavior Composite: r = 0.88) and inter-rater reliability (Communication skills: r = 0.75; Daily Living skills: r = 0.72; Socialization skills: r = 0.62; Motor skills: r = 0.78; Adaptive Behavior Composite: r = 0.74) have been reported.[48,89] Several items contained in the motor domain are very challenging for individuals with RTT. In a study developed to explore the relation between social impairments and clinical severity in RTT the authors used VABS excluding the Daily Living skills and the Motor skills domains due to motor impairment of participants (80 girls with RTT; mean age: 6.0 y, SD 3.4 y; range: 1.6–14.9 y).[95] Another study that aimed to describe the age-related clinical and behavioral change into adulthood in a group of 91 girls and women with RTT (mean age: 20.5 y; range: 4–47y) excluded the VABS from follow-up assessment as the authors did not consider this scale sensitive enough to detect the participants' change.[36] However, one study aimed to identify the characteristics of the anxiety-like behavior in RTT found a correlation between VABS motor domain and general anxiety and mood abnormalities in a sample of 74 girls with RTT (mean age: 5.35 y SD 2.36 y; range: 2–11 y).[33]

Functional Independence Measure for Children (WeeFIM)

WeeFIM is a measure of functional ability that can be used for typically developing children, aged 6 months through 7 years, as well as children with disabilities and delays in functional development over 7 years. It is an 18-item performance measurement system that documents self-care, functional mobility, and cognitive abilities.[96] WeeFIM measures disability, not impairment, the focus of measurement is on the degree of performance of tasks without relying on predeterminate criterion.[97] For each item, this scale provides a score between 1 (need for total assistance to perform the task) and 7 (task performed completely independently). The mobility domain includes five items: three for transfers (chair, wheelchair; toilet; tub, shower) and two for locomotion (walk, wheelchair, crawl; stairs). The chair and wheelchair transfer item includes all aspects of transferring to and from a chair or wheelchair comprising coming to a standing position if walking is the typical mode of locomotion. Toilet transfer item includes all aspects of transferring on and off a toilet. Tub and shower transfers include getting into and out of a tub or shower stall.

Walk, wheelchair, crawl locomotion task includes walking, once in a standing position; using a wheelchair, once in a seated position; and crawling on a level surface. Stairs locomotion task includes going up and down 12–14 stairs (one flight) indoors.[66] WeeFIM was used to describe the functional abilities of a group of 27 women with RTT (mean age: 40.7 y; median age: 43 y; range: 30–60 y).[56] A modified parent-report WeeFIM comprising 18 items scored on a 7-point scale was used to examine the effects of scoliosis surgery on functional outcome of a group of 16 females with RTT (mean age of scoliosis surgery: 13.73 y; range; 12.6–14.8 y).[43] However, WeeFIM showed a significant floor effects in one study aimed to relate functional outcomes to mutation type and age in a sample of 96 girls with RTT (mean age: 6.2 y; range: 5.4–7.0 y).[52]

Physical Abilities and Mobility Scale (PAMS)

PAMS is a 20-item quantitative scale designed to quantify progress toward gross motor therapeutic goals during rehabilitation intervention of children ages two and older. Items included in PAMS assess tolerance to positioning and orthosis or splinting, support needed for seating system, head and trunk control, ability to roll and stand, transition from supine to sit, from sit to stand, from floor to stand, into and out of a car and environmental transfers, assistive device needed for ambulation, distance of ambulation, level of assistance for ambulation, community ambulation skills, wheelchair mobility, standing balance, and stairs. PAMS was developed as a brief and repeatable measure of physical skills and mobility to complement WeeFIM by detecting subtle changes in a child's status, including items reflecting degree of caregiver burden, in relationship to goals for an inpatient rehabilitation admission.[71,90] Scoring for each item ranges from 1 (unable to complete the task) to 5 (able to complete in a normal manner); total possible score ranges from 20 to 100. Higher scores represent higher levels of function. PAMS demonstrates good reliability and validity as well as sensitivity to response to physical therapy and gross motor recovery in children with traumatic and acquired brain injuries. Moderate to high correlation was found between PAMS and WeeFIM.[60]

Pediatric Evaluation of Disability Inventory (PEDI)

The PEDI was developed by Haley et al.[70] The main purpose of this assessment instrument is to collect information about capacity, level of independence and extent of modification required to perform functional activities in the areas of self-care, mobility, and social function across 237 items. The age at which more than 90% of children are able to perform a particular activity is determined and validated. It is expected that over 90% of typical developing children can perform all activities of the PEDI after 8 years of age.[8] In a study for validation of functional mobility test for individuals with RTT it was used as a comparative measure.[12] The mobility subscale of PEDI includes: 59 functional skills items scored between 0 (unable or limited capacity to perform the task) to 1 (Capable of performing the item in most situations); seven items on caregiver assistance needed to perform mobility task scored between 0 (total assistance needed) and 5 (independent); seven items were modification of tasks resolution patterns (e.g., if no modification of the pattern occurs, the assessor reports "N"; if an extensive modification of the motor pattern was applied by the subject, the assessor reports "E").

Barthel Index (BI)

BI[73] is a 10-item measure of activities of daily living and functional outcomes. It has been developed for use at hospitals and to be assessed remotely or by self-assessment of patients.[54,98,99] In clinical activity it is widely used with subjects survived after score and, in general, with elderly individuals with disabilities.[100–102] BI included items to evaluate subject ability in: personal toilet and bathing himself (scored 0 or 5); feeding, getting on and of toilet, ascend and descend stairs, dressing, bowel control, and bladder control (scored 0, 5, or 10); walking on level surface (scored 0, 10, or 15); and moving to and from bed (scored 0, 5, 10, or 15) .[103–111] The best score is 100 (normal function) and the worst score 0 (patients without any ability of self-preservation).[54]

Discussion

The aim of the present review is to describe clinical evaluation tools used to assess motor functioning and musculoskeletal abnormalities of patients with RTT. As shown in the last decade, different research groups have employed several evaluation tools to assess gross motor ability, mobility functioning, muscle tone and amount of physical activities in RTT. The RTT-specific gross motor tools described in this review show different strengths and weaknesses. With reference to the advantages of RSCMS, it is widely used in clinical and scientific practice and is a good instrument to study motor impairment of RTT population. In addition, the video for compiling the RSGMS can be recorded by parents and delayed scored by clinicians thus facilitating data collecting. Despite the strengths of RSCMS, RESMES and RFES are more suitable for use in a rehabilitative setting as they investigate motor function on a finer grain scale. In particular, RFES evaluates more motor skills than RESMES and could be more sensitive to change after rehabilitation treatment. However, it shows a limitation compared to other two tools, because RSGMS and RESMES are available in the attachment to the refereed articles whereas RFES should be requested directly from the author. In general, considering the three described tools, RFES can be regarded as an effective gross motor assessment tool in RTT population.

With reference to daily physical activity measurement tools, electronic devices, such as inertial sensors, allow precise and remote measurement of the daily physical activities of subjects with RTT. SAM has demonstrated higher accuracy compared with other physical activity devices in free-living conditions, across a range of walking speeds, both in healthy subjects and RTT population. On the other hand, ActivePAL™ can precisely measure the amount of sedentary time of individuals with RTT. Both these devices present with different strengths and some limitations, because they have a high cost which can complicate their use in clinical settings. In contrast with these two tools, mBAR is a cheaper way to assess the physical activity in RTT population. It is slightly less accurate

in the evaluation of sedentary time compared with ActivePAL™, but its data are comparable with those measured with electronic devices. Moreover, the mBAR score is capable of predicting the number of steps taken by independent walkers.

As regards to the RTTspecific severity scale, the scales described in this review show shortcomings in the gross motor abilities assessment because they are not designed to accurately evaluate gross motor abilities of subjects with RTT, but they offer some interesting reflections in this field. For example, the authors of all these scales have chosen to insert at least two items on muscle tone or musculoskeletal or extremities growth abnormalities in their evaluation tools. This suggests that the researchers consider these motor conditions a full part of the clinical severity picture of subjects with RTT. However, only a tool evaluates the muscle condition. It is well known that in RTT population muscle tone tends to change across a life span from an initial condition of hypotonia to a condition which progressively evolves into a rigid hypertonia in the elderly.[62,112] In addition, subjects with RTT show a wide range of muscle tone abnormalities which can vary also in the same subject between, for example, trunk and limbs, from hypotonia to hypertonia. Nevertheless, there is still a need for muscle tone evaluation tools that can comprehensively consider the high variability of muscle tone abnormalities in this population.[113–115] For these reasons, we remark that it is fundamental to include specific mobility items in assessment tools and the researchers should take into account the muscle and skeletal condition in the motor functioning assessment of subjects with RTT.

With reference to muscle condition evaluation tools, MAS evaluates spasticity and hypertonia but does not offer the possibility to score hypotonia. Whereas RTTRD[19] represents a valid tool in order to measure muscle tone abnormalities in RTT population using the muscle tone score proposed in ISS by Kerr and colleagues.[63]

With reference to functional mobility tests, we have described two tools: the FMS-RS and 2MWT. They are effective examples of how existing functional tests can be adapted to the peculiar characteristics of people with RTT. Both instruments are useful to measure global effects of therapeutic training, clinical trial and evolution of motor function in this population. They present strengths because they can be used to evaluate global functional outcome of rehabilitative intervention aimed to improve walking abilities of subjects with RTT.

As regards nonspecific evaluation tools, they are used in RTT in order to determine functional status related to several parameters in cross-sectional designs. WeeFIM and PAMS allow comparison with the general population but may not always be suitable for individuals with RTT. However, these two scales have the potential to measure functional changes after rehabilitative treatments and interventions.

Considering the inter-rater agreement properties of each scale described in this review, they present with different strengths and limitations. The inter-rater agreement is an important property because high inter-rater agreement provides reliability, and only tools with such property should be routinely used in the clinical practice.[116,117] High reliability means that a measurement is reproducible over time, in different settings and by multiple raters.[118] The reliability is due to the agreement among different observers, called inter-rater reliability, and to the agreement of repeated measurements performed by the same observer, called intra-rater reliability.[118] In the clinical field, measurements, diagnoses, and assessments are habitually performed by different clinicians; even if they use the same questionnaires, psychometric scales, and diagnostic tests the subjectivity is an open issue. As Marasini, Quatto, Ripamonti[116,117] stated, it is fundamental to have at disposal statistical methods aimed to assess the quality of measurement of these instruments. Two approaches to analyzing method agreement are widely used: Cohen's kappa and Fleiss' kappa coefficients. The first is limited to two raters and categorical variables; the observed agreement is corrected for the agreement expected by chance. The second is a generalization of kappa coefficient in the case of multiple observers and categories. Marasini, Quatto, Ripamonti[116,117] have proposed an alternative measure for inter-rater agreement and to resolve the limitations of the kappa statistic, both in Cohen's and in Fleiss' version, it is a modification of Fleiss' kappa generalized to the case of ordinal variables.

The inter-rater agreement properties of the scales described in the present review have not been checked or they have been investigated using statistical tools such as Cohen's kappa, which present a paradoxical behavior.[116,117] The statistic proposed by Marasini, Quatto, Ripamonti[116] has never been applied. Considered the importance of a high inter-rater agreement in clinical practice, as well above discussed, for clinicians it is important to know the properties of each scale. In this regard, RSGMS and RESMES have been validated on a statistical representative sample while RFES has only been used in case studies. SAM, ActiPAL, and mBAR show good accuracy indices but there is still the need to establish and standardize specific accelerometer protocols for measuring physical activity level in subjects with RTT.[59] Future studies on the use of these scales should be carried out to prove reliability across repeated measures in longitudinal designs. Also, Rett specific severity scales present good reliability and validity, but they do not measure precisely the muscle tone. Finally, among the nonspecific assessments considered in this review, reliability of WeeFIM and PAMS[71] needs to be tested in longitudinal designs to assess whether these scales are sensitive enough to measure functional change after therapeutic interventions or disorder evolution with age.

The current review has some limitations. Firstly, only articles published between 2009 and 2019 have been analyzed. Scientific literature on effective therapeutic interventions to improve gross motor function of these persons remains poor.[30,52,98,99] Given that subjects with RTT present complex motor disabilities and functional limitations, motor evaluations in this population should rely on accurate and specific assessment of all motor components to allow clinicians to identify significative and functional objects for rehabilitative and preventive interventions.[37,119–122] Secondly, the statistical characteristics are not available for all the included tools, for this reason we do not compare these parameters across the

examined assessments. Thirdly, the evaluation tools do not refer to a specific population such as RETT syndrome's population, consequently the characteristics of sex, age and the context of study are different. This could create problems in terms of generalization.

In conclusion, this review underlies the lack of adequate evaluation tools to assess musculoskeletal abnormalities and deformities in this population. The absence of these assessments could be due to a statistical difficulty as it is challenging to build an evaluation tool that can score the entities of the abnormalities related to the amount of disability they cause. The building of a comprehensive motor evaluation protocol for motor impairment of individuals with RTT is needed to allow professionals working with these people to have an overview of all the elements which influence their mobility and to apply adequate and significative intervention.[123,124] Appropriate functional evaluation tests represent an interesting manner to collect significant data to be used in clinical trials and rehabilitative settings both in RTT and other disabilities.[43,56,125,126,127,128]

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Compliance with Ethical Standards

The authors declare no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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