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Building the repertoire of measures of walking in Rett syndrome

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Keywords: Rett syndrome, walking, Functional Mobility Scale, Two-minute walk test
Abstract

Background: The repertoire of measures of walking in Rett syndrome is limited. This study aimed to determine measurement properties of a modified 2-minute walk test (2MWT) and a modified Rett syndrome-specific Functional Mobility Scale (FMS-RS) in Rett syndrome.

Methods: Forty-two girls and women with Rett syndrome (median 18.4 years, range 2.4-60.9 years) were assessed for clinical severity, gross motor skills and mobility. To measure walking capacity, twenty seven of this group completed a 2MWT twice on two different assessment days. To assess walking performance, the FMS-RS was administered to the total sample of parents (n=42) on two occasions approximately one week apart.

Results: There were negative correlations between clinical severity and 2MWT (r = -0.48) and FMS-RS (r = -0.60--0.66). There were positive correlations between gross motor skills and mobility and 2MWT (r = 0.51, 0.43) and FMS-RS (r = 0.71–0.93, 0.74-0.94), respectively. Test-retest reliability for the 2MWT was good with high intra-day and inter-day correlations (ICC=0.86-0.98). For the 2MWT, the standard error of measurement was 13.8m and we would be 95% confident that changes greater than 38m would be greater than within subject error. There was good test-retest reliability for all three distances on the FMS-RS (ICC=0.94-0.99).

Conclusions: Walking capacity as measured by the 2MWT showed expected but limited relationships with measures of different constructs, providing some support for concurrent validity. Walking performance as measured with the FMS-RS was more strongly consistent with other clinical measures supporting its concurrent validity. Test-retest reliability was good for both the FMS-RS and the 2MWT. Therefore these measures have the potential to be used in clinical practice and research.

Abbreviations

CP: Cerebral palsy
CSS: Clinical Severity Scale
FMS: Functional Mobility Scale
FMS-RS: Functional Mobility Scale – Rett syndrome
HAS: Hoffer Ambulation Scale
MDD: Minimal detectable difference
PEDI-m: Pediatric Evaluation of Disability Inventory –mobility
RSGMS: Rett syndrome Gross Motor Scale
RTT: Rett syndrome
SEM: Standard error of measurement
2MWT: Two Minute Walk Test
Introduction

Rett syndrome (RTT) is a neurodevelopmental disorder which mainly affects females. The incidence is approximately 1 per 9,000 females [1] and as such it is considered to be one of the commonest genetic causes of severe intellectual disability in females [2]. From birth the development is normal or slightly delayed and there may be subtle signs of disease but after 6-18 months of life there is a period of developmental stagnation and loss of many acquired skills [3, 4]. Typical RTT is characterized by the regression or loss of purposeful hand use and spoken language, development of abnormal gait or absent gait and hand stereotypies [5]. Mutations in the gene encoding Methyl-CpG-binding protein 2 (MECP2) has been identified as the cause of RTT in the majority of cases [6]. For most mutations, clinical severity increases with age [7]. Whilst mortality is increased, many live into adulthood and some into older age [8, 9].

In general, the gross motor repertoire is limited in RTT. A large proportion of individuals with RTT are able to sit independently and about half are capable of walking 10 steps or more independently or with minimal support [10, 11]. Many experience difficulties with transitions and only a small proportion is capable of performing more complex activities like stepping over an obstacle or walking on a slope independently [11]. Walking is a common physical and participation-based activity in adults with intellectual disability [12]. It has been suggested that participation-based activities have a positive impact on quality of life in children with disabilities [13] including those with RTT [14]. Furthermore, a recent study on survival in RTT showed that, among other characteristics, poorer motor capacity was associated with earlier mortality [9]. These findings suggest that focus on the maintenance of walking and promotion of an active lifestyle throughout life could be valuable for the health and quality of life of individuals with RTT [9, 15].

In Australia, researchers have developed and validated measures of gross motor capacity [11, 16] and gross motor performance [15, 17] which include walking. A specific measure of functional walking capacity and a brief measure of walking performance have not yet been reported in RTT. Building the repertoire of walking measures is extremely valuable to understand and explain how the walking abilities are affected. Furthermore validated measures are important as outcome measures in clinical trials and interventions [15]. However, development of new or modifications to existing measures are likely to be needed due to the unique traits of RTT (e.g. altered self-initiation of movement, limited comprehension of verbal instructions).

The six minute walk test (6MWT) measures the maximal distance walked over six minutes and has frequently been used to assess walking capacity in adults with intellectual disability and in children with CP [18-20]. Alternatively, a two minute walk test (2MWT) has been proposed for populations with more limited capacity to walk [21-23]. Good intra-rater and inter-rater reliability of the 2MWT have been described in the elderly and following stroke [23, 24] and excellent test-retest has been found in a general population [25]. In individuals with RTT, fatigue and motivation could play an important role in the assessment of functional capacity, and therefore whilst a 2MWT could be of value, it is likely that modifications would be necessary to increase compliance and enable optimal achievement.

The Functional Mobility Scale (FMS) is a measure of everyday walking performance over different distances and in different settings for children with cerebral palsy (CP) [26]. Construct and concurrent validity and inter-rater reliability of the FMS has been
established in children with cerebral palsy and it was translated into Danish in 2010 [26-28]. The FMS has been proposed as a useful scale in other disabilities [27]. As individuals with RTT rarely use handheld walking aids as a mean of independent walking and they are unable to propel a manual wheelchair independently, a scoring system specific to RTT is needed.

The aims of this study were two-fold: 1) 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.

Methods

Participants

At the time of recruitment 108 individuals were diagnosed with RTT in Denmark, 94 of whom had a pathogenic MECP2 mutation. Approximately 60% of those individuals with a pathogenic MECP2 mutation had some capacity to walk on a daily basis. Forty-two girls and women with RTT and a MECP2 mutation who visited the Danish Rett Syndrome Center in the study period were invited to participate in the study. To be eligible to participate in assessments with the 2MWT individuals needed to be functional ambulators (level I and II on the Hoffer Ambulation Scale) [29, 30] and residing in the Capital Region or Region Zealand in Denmark.

The study was approved by the Capital Regional Committee on Health Research Ethics (H-6-2014-074) and parents or other caregivers provided written informed consent to participate in this study.

Measures

Modified walking measures

Modified 2-minute Walk Test
The individual with RTT walks back and forth between two cones on a 20 meter track for two minutes and the total distance covered is measured. Several modifications to the 2MWT were made to enhance comprehension, motivation and maximal effort for RTT (see Appendix I). The modified 2MWT 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 for the person to keep her balance and to maintain the highest possible gait speed.

Rett syndrome-specific Functional Mobility Scale
The Functional Mobility Scale – Rett Syndrome (FMS-RS) has been modified from the FMS with permission from the Hugh Williamson Gait Laboratory, The Royal Children's Hospital, Melbourne, Australia (see Appendix II). FMS-RS assesses walking performance
over three distances: 5m, 50m, and 500m corresponding to home ambulation, day center ambulation and community ambulation, respectively. The scoring system in the FMS-RS refers to the level of assistance needed to walk the given distance. A score of 0-4 is given at each distance with 0 defined as “unable” and 4 as “independent”. The scoring system is an expansion of that used in the RSGMS developed by Downs et al [11].

**Comparative clinical measures**

**Clinical Severity Score (CSS)**

The CSS is a RTT-specific scale consisting of 13 items describing early development and current clinical characteristics with a maximum score of 58 indicating greater severity (31).

**Rett Syndrome Gross Motor Scale (RSGMS)**

The RSGMS is a RTT-specific outcome measure of gross motor skills including sitting, standing, walking and transfer skills [11]. Fifteen items are rated on a four-point scale and a maximum score of 45 indicates better gross motor skills.

**Pediatric Evaluation of Disability Inventory (PEDI)**

The PEDI describes functional skills in children with a disability and their need of caregiver assistance [32] and a Danish version has been validated [33, 34]. For the purposes of this study the Mobility-Caregiver assistance subscale (PEDI-m) was used with higher scores indicating greater independence.

**Procedures**

Data collection took place between May-June 2014 and May-July 2015. The CSS and the PEDI-m were administered by observation and interview. The RSGMS was scored from direct observation. The FMS-RS was assessed on the basis of a short interview with parents-caregivers and was administered twice within approximately 1 week. The first FMS-RS assessment took place on the day of the visit at the center and the second assessment was completed by telephone interview by the first author. Participants who were functional ambulators were assessed twice with the 2MWT on each of two separate occasions. The 2MWT assessments took place in the pre-school, school, day-time activity center or in the home of the participants according to the preferences of the parents/caregivers. To quantify the test-retest reliability and to determine a potential learning effect of the 2MWT, the test was administered twice on the same day with a short break between tests. During assessments participants wore a Polar RCX3M heart rate monitor (Kempele, Finland). Before testing, the resting heart rate was noted after 5 minutes of relaxed sitting. Between tests participants sat down during the break until the resting heart rate was reached. This testing procedure was repeated within approximately 1 week. All assessments and interviews were performed by the same two experienced physical therapists with a background in pediatrics.
Analyses

Relationships between the 2MWT and FMS-RS walking measures and the clinical measures were assessed using the Spearman rank correlation test. Intraclass correlation coefficients (ICC) were calculated to determine test-retest reliability. Repeated measures analysis of variance (ANOVA) was used to identify differences in distances walked on the 2MWT by occasion (Day 1: test 1, test 2; Day 2: test 3, test 4). Following ANOVA a priori planned contrast tests were performed to detect a possible learning effect on the same day and between assessment days (test 1 vs test 2, test 2 vs test 3, test 2 vs test 4, test 3 vs test 4). To determine the absolute agreement for the 2MWT, the standard error of measurement (SEM) and the minimal detectable difference (MDD) [35] were calculated using the most consistent pair of test trials. SEM is defined as the square root of the mean square within-subjects error using repeated measures ANOVA and MDD is SEM×√2×1.96. Multiple linear regression was used to test whether age and gross motor skills predicted distance walked measured with the 2MWT. A p value <0.05 denoted statistical significance. Statistical analysis was conducted using SPSS (version 19.0).

Results

Forty-two girls and women aged 2.4 - 60.9 years (median 18.4 years) participated in this study. Each of the common mutation categories were represented. Sample characteristics and summary scores of the clinical measures are shown in table 1. Ambulation level was classified according to Hoffer Ambulation Scale (I. Community ambulator, walks indoors and outdoors; II. Household ambulator, walks indoors; III. Therapeutic ambulator, walks in therapy sessions/with parents; IV. Non-ambulant/stander, requires a wheelchair but is able to stand; V. Non-ambulant, requires a wheelchair) [30]. The majority of the participants were functional ambulators (n=31, 73.8%) and the remaining participants where either therapeutic ambulators (n=4, 9.5%) or non-ambulators (n=7, 16.7%). A subgroup of 27 girls and women aged 3.8 - 60.9 years (median 27.4 years, inter-quartile range (IQR) 15.8, 39.8) who were all functional ambulators participated in the 2MWT assessments.
Table 1. Sample characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All participants, n=42</th>
<th>Functional ambulators, n=27</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> median (IQR)</td>
<td>18.4 (7.2, 35.5)</td>
<td>27.4 (15.8, 39.8)</td>
</tr>
<tr>
<td><strong>Mutation</strong> n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-terminal</td>
<td>5 (11.9)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Early truncating</td>
<td>2 (4.8)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Large deletion</td>
<td>4 (9.5)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>p.Arg106Trp</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>p.Arg133Cys</td>
<td>1 (2.4)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>p.Arg168*</td>
<td>3 (7.1)</td>
<td>0</td>
</tr>
<tr>
<td>p.Arg255*</td>
<td>1 (2.4)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>p.Arg270*</td>
<td>1 (2.4)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>p.Arg294*</td>
<td>5 (11.9)</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>p.Arg306Cys</td>
<td>2 (4.8)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>p Thr158Met</td>
<td>12 (28.5)</td>
<td>10 (37.0)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (11.9)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td><strong>HAS</strong> n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community ambulator</td>
<td>28 (66.7)</td>
<td>24 (88.9)</td>
</tr>
<tr>
<td>Household ambulator</td>
<td>3 (7.1)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Therapeutic ambulator</td>
<td>4 (9.5)</td>
<td>0</td>
</tr>
<tr>
<td>Non-ambulant/stander</td>
<td>6 (14.3)</td>
<td>0</td>
</tr>
<tr>
<td>Non-ambulant</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td><strong>CSS</strong> median (IQR), (n=38/23)</td>
<td>20 (17, 23)</td>
<td>18 (15, 21)</td>
</tr>
<tr>
<td><strong>RSGMS</strong> median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=39/24)</td>
<td>31 (16.8, 36.8)</td>
<td>34 (27, 40)</td>
</tr>
<tr>
<td><strong>PEDI-m</strong> median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=39/24)</td>
<td>47.2 (29, 61.1)</td>
<td>52.4 (45.8, 62.6)</td>
</tr>
</tbody>
</table>

HAS, Hoffer Ambulation Scale; CSS, Clinical Severity Score (maximum score of 58 with higher scores indicating greater severity); RSGMS, Rett Syndrome Gross Motor Scale (maximum score of 45 with higher scores indicating greater motor skills); PEDI-m, Pediatric Evaluation of Disability Inventory-mobility (maximum score of 100 with higher scores indicating greater independence)

2MWT (n=27)

All 27 participants completed the 2MWT assessments twice on the first day although one girl refused to complete the assessments the second day. Assessments were performed a mean of 6.96 (SD 4.75) days apart. The majority of the girls needed minimal or moderate support to walk continuously without losing balance, e.g. held in one hand (n=12), walk assistant held the participants hand and elbow or walked in front of the girl with two hands held (n=12). Three of the participants walked with standby supervision to maintain walking along the track. Four of the participants required strategic motivators to complete the assessments (favorite music n=2, favorite snack n=2). The mean heart rate in relaxed sitting and the working heart rate after the second test were 91(SD 15) and 118.7(SD 19.4) respectively on test day one and 90(SD 16) and 119.2(SD 16) respectively on test day two. On average participants had a break of 4.8(SD 1.4) minutes between trials on the first assessment day and 4.1(SD 1.1) minutes the second day.
Table 2. Spearman rank correlation matrix

<table>
<thead>
<tr>
<th></th>
<th>2MWT</th>
<th>FMS-RS 5</th>
<th>FMS-RS 50</th>
<th>FMS-RS 500</th>
<th>CSS</th>
<th>RSGMS</th>
<th>PEDI-m</th>
</tr>
</thead>
<tbody>
<tr>
<td>2MWT</td>
<td>1</td>
<td>0.52</td>
<td>0.38</td>
<td>0.36</td>
<td>-0.48</td>
<td>0.51</td>
<td>0.43</td>
</tr>
<tr>
<td>FMS-RS 5</td>
<td>0.52</td>
<td>1</td>
<td>0.90</td>
<td>0.70</td>
<td>-0.60</td>
<td>0.90</td>
<td>0.84</td>
</tr>
<tr>
<td>FMS-RS 50</td>
<td>0.38</td>
<td>0.90</td>
<td>1</td>
<td>0.70</td>
<td>-0.66</td>
<td>0.93</td>
<td>0.94</td>
</tr>
<tr>
<td>FMS-RS 500</td>
<td>0.36</td>
<td>0.70</td>
<td>0.70</td>
<td>1</td>
<td>-0.61</td>
<td>0.71</td>
<td>0.74</td>
</tr>
<tr>
<td>CSS</td>
<td>-0.48</td>
<td>0.70</td>
<td>-0.66</td>
<td>-0.61</td>
<td>1</td>
<td>-0.76</td>
<td>-0.73</td>
</tr>
<tr>
<td>RSGMS</td>
<td>0.51</td>
<td>0.90</td>
<td>0.93</td>
<td>0.71</td>
<td>-0.76</td>
<td>1</td>
<td>0.92</td>
</tr>
<tr>
<td>PEDI-m</td>
<td>0.43</td>
<td>0.84</td>
<td>0.94</td>
<td>0.74</td>
<td>-0.73</td>
<td>0.92</td>
<td>1</td>
</tr>
</tbody>
</table>

2MWT, 2 Minute Walk Test; FMS-RS, Functional Mobility Scale – Rett Syndrome; CSS, Clinical Severity Score; RSGMS, Rett Syndrome Gross Motor Scale; PEDI-m, Pediatric Evaluation of Disability Inventory-mobility.

A negative correlation was seen between 2MWT distance and clinical severity ($r = -0.48$), whereas positive correlations were seen in relation to gross motor skills ($r = 0.51$) and mobility ($r = 0.43$), (see table 2). Summary scores of the 2MWT at the four time points are shown in table 3. Repeated measures ANOVA demonstrated a significant difference among the mean values ($F = 17.09, p < .001$).

Table 3. Summary scores of the 2MWT (distance)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test 1</td>
<td>75.97</td>
<td>30.16</td>
<td>20.1-127.9</td>
</tr>
<tr>
<td>Test 2</td>
<td>83.07</td>
<td>27.57</td>
<td>28.5-132.2</td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test 3</td>
<td>83.67</td>
<td>24.23</td>
<td>34.7-132.9</td>
</tr>
<tr>
<td>Test 4</td>
<td>87.13</td>
<td>25.75</td>
<td>38.9-140.0</td>
</tr>
</tbody>
</table>

Planned contrasts of the four test occasions and ICC values are shown in table 4. The mean distance walked during test 1 was on average eight metres shorter than during test 2. The subsequent comparisons of distances walked were not significantly different although on the second test day, the mean distance walked was also shorter at the first assessment. Test-retest reliability of the 2MWT between trials on the same day and between days was good with high ICC values (table 4).

Table 4. Comparisons of means between 2MWT test occasions and ICCs

<table>
<thead>
<tr>
<th>Test occasions</th>
<th>F</th>
<th>p</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 vs 2</td>
<td>4.85</td>
<td>0.03*</td>
<td>0.95</td>
</tr>
<tr>
<td>2 vs 3</td>
<td>0.10</td>
<td>0.76</td>
<td>0.88</td>
</tr>
<tr>
<td>2 vs 4</td>
<td>1.87</td>
<td>0.18</td>
<td>0.86</td>
</tr>
<tr>
<td>3 vs 4</td>
<td>1.10</td>
<td>0.30</td>
<td>0.98</td>
</tr>
</tbody>
</table>

*p < 0.05

To determine absolute reliability, SEM and MDD were calculated on the basis of the second trial, after learning had occurred, from each assessment day (test 2 and 4) to account for week to week variation. The SEM was 13.8m and the MDD 38m, which indicates that an observed difference on distance walked by the same individual should at least be 38m to be 95% confident that the difference is greater than within subject
measurement error. Lastly, linear regression indicated that gross motor skills \((t = 3.41, p = 0.002)\) but not age \((t = -0.25, p = 0.8)\) was a strong predictor of the distance walked on the 2MWT.

**FMS-RS \((n=42)\)**

FMS-RS had moderate to strong correlations with all the measures, which supports the concurrent validity of the FMS-RS (table 2). Negative correlations were seen in relation to clinical severity \((r = -0.60--0.66)\) and positive correlations were seen in relation to gross motor skills \((r = 0.71--0.93)\), and mobility \((r = 0.74--0.94)\). In table 5 the distribution of FMS-RS rating on the two test days is shown. At day 1, 66.7% of the participants required minimal/no assistance to walk 5m, 7.1% required moderate assistance and 26.2% were unable/required maximal assistance. For 50m, this proportion remained nearly the same. However for 500m, approximately half were independent/required minimal assistance and half of the participants were unable to perform this task. The FMS-RS was administered twice within a mean of 8 days (SD 4.37). Reliability of the two FMS-RS ratings was strong with high ICC values across each of the distances (table 5).

Table 5. Distribution of FMS-RS ratings and ICCs

<table>
<thead>
<tr>
<th>Scale</th>
<th>Rating*</th>
<th>Day 1 ((n))</th>
<th>Day 2 ((n))</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMS-RS 5</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>21</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>FMS-RS 50</td>
<td>0</td>
<td>9</td>
<td>9</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>11</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>15</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>FMS-RS 500</td>
<td>0</td>
<td>21</td>
<td>19</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
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<tr>
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<td>3</td>
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<td>11</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

*0=unable, 1=maximal assistance, 2=moderate assistance, 3=minimal assistance, 4=independent

**Discussion**

To expand the range of possible measures to assess walking capacity and performance in RTT, two existing measures were modified to be more appropriate for RTT – the 2MWT and the FMS. Initial assessment of the clinimetric properties supported the concurrent validity and test-retest reliability of both measures.

The 2MWT was modified as it has been shown that motivation and task understanding are factors which affect fitness results in adults with intellectual disability [36, 37]. Individuals with RTT have severe dyspraxia which limits the execution and self-initiation of movements. Additionally, many experience poor balance and therefore need physical
support to walk. For these reasons it was chosen to use a walk assistant during assessments. Preferably, it should be the same assistant in all tests. Unfortunately, in seven of the participants this was not possible due to staff schedules and this could explain some of the variation seen. All modifications to the 2MWT were applied in a standardized and consistent manner and other studies in children with CP and adults with intellectual disability have made similar modifications (e.g. visual goals, use of a pacer, more frequent standardized encouragement, and familiarization) [18, 19]. This modified 2MWT is a first attempt to measure walking capacity in RTT. Due to limited communication and cognitive skills, participants were not asked about their perceived exertion and the 2MWT was not validated against a maximal exercise criterion due to issues of fatigue, motivation and neuromuscular and/or musculoskeletal impairments seen in people with multiple disabilities [37]. Thus, the 2MWT might not reflect the true capacity in girls and women with RTT. However, the correlations found between 2MWT and the other measures of severity, gross motor skills and mobility were low to moderate which was expected as the 2MWT likely represents a somewhat different domain. This provides initial support for the concurrent validity of the 2MWT. Overall, the 2MWT seemed feasible in the usual setting of the participants and only few needed strategic motivators to walk which could indicate that they did not get bored, frustrated or fatigued by the test. In this study a 20m track with 180° turns was used. In future studies with individuals with RTT it is important to be aware of this aspect, as walking in a square track with 90° turns or on a continues track could have an impact on the distance walked [38]. Regarding the possible learning effect during repeated walking trials, studies in other clinical populations report different results [20, 21, 39] whereas in our study, a significant learning effect was seen between the first and second test on the first assessment day. This result indicates the need of performing a practice trial prior to data collection in girls and women with RTT.

The FMS includes walking on uneven surfaces, curbs and stairs and as such it measures independent mobility. The intent of the FMS-RS is however to focus on walking on level ground since advanced mobility skills are generally limited in people with RTT [11]. It is recognized that walking outside might require some negotiation with different surfaces. If a more comprehensive description of the gross motor skills is needed the RSGMS should be used [11]. In the standard FMS the children are not allowed to be assisted by another person. Only a minority of persons with RTT is able to use walking aids due to their dyspraxia and limited hand use and thus they are dependent on assistance from their parents or other caregivers. Due to these differences modifications of the FMS were considered a prerequisite to enable assessment of walking performance within a similar framework. Results showed moderate to high correlations between FMS-RS and the other measures of severity, gross motor skills and mobility. Both CSS and RSGMS are RTT-specific measures and it seems reasonable that correlations are higher in RSGMS which measures gross motor skills whereas CSS incorporates many different functional and clinical characteristics in RTT including ambulation, hand use and epilepsy. PEDI-m is generic and focuses on daily mobility tasks such as bed transfers, ambulation indoors and walking up/down stairs and these correlations also support the validity of the FMS-RS. For all measures the lowest correlations were seen in FMS-RSS500. Given the distances walked on the 2MWT it is not unexpected that very few participants are able to walk approximately 500m within the community. In general, FMS-RS is a simple measure to use and provides a varied picture of the assistance needed to ambulate in different environments. Our knowledge about decline in walking in RTT needs to be increased as ambulation has a positive association with survival [9]. In RTT FMS-RS can provide detailed longitudinal information on daily
ambulation which could be helpful in the understanding of associations to a possible decline in walking. Previously, FMS has been used to describe recovery in children with CP following single-event multilevel surgery and has been found to be responsive to change [26]. The same could be anticipated with the use of FMS-RS following spinal fusion [40] and other orthopedic surgeries in RTT. This and the possible use of the FMS-RS in other habilitation interventions remain to be determined.

Test-retest reliability of the 2MWT and the FMS-RS was found to be good with high ICC values. The mean two minute distances walked by the participants in this study (75.97–87.13m) are substantially shorter than those normative data published in healthy women aged 80-85 years (134.3m) [41]. At the present time values in clinical populations have only been reported for the 6MWT, which involves distances not appropriate for individuals with RTT [18, 19, 39]. The closest comparison is with children with CP at GMFCS level III, whose mean distance on the 6MWT was 240.2m (~84.9m on a 2MWT) [19]. The moderate increases in heart rate during the 2MWT suggest that in this sample of functional walkers with RTT, walking was not associated with maximal effort indicating a potential to walk faster or for longer distances. Further studies in RTT are warranted to clarify these relationships. In terms of absolute reliability in the 2MWT, the MDD was found to be 38m. For healthy adult women aged 18-85 years the MDD has been found to be 33.4m [41]. For individuals with RTT, a change of less than 38m could however still reflect a clinical important difference as a change of 38m will correspond to more than a doubling in distance walked in some individuals. We have estimated the MDD value for the 2MWT to indicate the scope of within subject error but we acknowledge the importance of further research to investigate minimally important change (MIC) values for this group [42].

This study is limited by the sampling method which yielded a sample where the majority of participants were functional walkers (73.8%). In general, cohort studies show that slightly less than half of the population with a clinical diagnosis of RTT are able to walk [10, 11]. The total sample did however include 44.7% of the Danish population of girls and women with RTT and a MECP2 mutation. In addition, the subgroup of participants performing the 2MWT assessments was small in number and only included those who were functional ambulators. On the other hand with respect to the Danish population of people with RTT the subgroup size seems reasonable. In our clinical experience, some of the therapeutic ambulators would not be able to walk for 2 minutes.

In conclusion, concurrent validity and test-retest reliability of the 2MWT and FMS-RS were established. Both measures have the potential to be valuable tools for researchers and practitioners. Together with information about gross motor skills (11) and physical activity level [15], the 2MWT and FMS offer a comprehensive understanding of capacity, everyday function and mobility in girls and women with RTT. In this study, gross motor skills but not age had a significant impact on the walking capacity as measured by the 2MWT. In RTT, walking capacity and walking performance are likely limited by both physical factors (gross motor skills, aerobic fitness) and environmental factors, since the majority of persons with RTT are dependent of the people around them to walk. These relationships need to be studied further. Additional studies are needed to determine whether the MDD of 38m on the 2MWT is achievable following an intervention or if smaller changes would be considered to be a clinically important difference. Likewise, future studies should address the applicability of the FMS-RS as an outcome measure in both orthopedic and habilitation interventions.
Acknowledgements

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Declaration of Interest

The authors report no conflicts of interest.
Appendix I

Modified 2-minute walk test (2MWT)
- to be used in people with Rett syndrome

Description
The test assesses how far (metres) a person can walk in 2 minutes. It requires 2 assessors (Assessor 1 keeps track of the timing, provides feedback, walks next to the person; assessor 2 counts laps, provides motivators if needed, provides a chair if needed) and 1 walk assistant who knows the person well (e.g. parent, therapist, teacher). The walk assistant provides the necessary support (one-hand/two-hand/trunk support) in order for the person to maintain balance and to keep the velocity as high as possible.

Equipment
A walking track which is 20 in length, two cones, a stopwatch, tape, and a chair. (A measuring wheel and a mechanical lap counter could be used).

Preparation
Place a cone in each end of the walking track. A minimum of 1½ metres from the cone to the end wall is required to allow the person to walk around the cone. The walk test is performed together with a well-known walk assistant who supports the person. The person might also use a walking aid. Keep a chair ready if the person needs to sit. A common strategy as to how to support and motivate the person is planned before the assessment. The strategy is planned through questions to the walk assistant.

Strategy
How much support does she need to walk 10 metres?

☐ None  ☐ One-hand support  ☐ Two-hand support  ☐ Trunk support

How much support does she need, when you have to walk from point A to B (a route decided by you)?

☐ None  ☐ One-hand support  ☐ Two-hand support  ☐ Trunk support  ☐ Other:________________________

Does she use a walking aid?

☐ No    ☐ Yes, which one:________________________

What usually motivates her when she does not want to walk any further?

☐ Music, what:________________________

☐ DVD, which:________________________

☐ Fluids, what:________________________

☐ Food, what:________________________

☐ Other, what:________________________

Instruction for the person and walk assistant (in italic)
The person stands with her toes at the starting line together with the walk assistant. Assessor 1 stands next to them. Assessor 1 provides instructions and feedback. The walk assistant should
not speak with the person during the walk test. Assessor 2 stands at the other end of the walking track and has the chosen motivators ready in case they are needed (e.g. favorite music, favorite cartoon). If these motivators are needed, assessor 2 will walk 5 metres ahead of the person in order for the person to see/listen to the motivators.

We are going to find out how far you can walk in 2 minutes. You have to walk back and forth between the cones together with your walk assistant.

We have placed one cone here at the starting line and one cone in the other end which you can walk around when you need to turn and walk back.

When I say READY-SET-GO the walk test will start and you have to walk as far as possible. If you need it, you can take a break during the test.

When I say STOP you have stand still until I have put some tape in front of your toes.

Do you have any questions? Are you ready?

READY-SET-GO

After 30 seconds: You are doing really good!
After 1 minute: Great! Keep walking – you have 1 minute left
After 1 minute 30 seconds: You are doing really good!
After 1 minute 45 seconds: Keep walking, you only have 15 seconds left

If the person needs a break during the test she is offered the chosen fluids or food. After a 10 second break and if necessary after 20 seconds:
Continue to walk – you are doing great
The test will be discontinued if the person will not walk after a 30 second break.

Timing and counting
The number of laps will be registered during the test by assessor 2. The remaining distance is measured (metres from the last cone to the stop point) and the total distance is calculated (number of laps + remaining distance).

Length of the walking track:_________

Number of laps:_________

Remaining distance:_________

Result
Date:_________ Time:_________ Distance:_________ metres

Number of breaks:_________ Number of seconds where the person stands still:_________ sec

Age:_________ □Male  □Female

Name of the walk assistant:_____________________

Comments (ask the walk assistant)
What might have affected the test result? (e.g. sleep, pain, motivation, mood, time of the day, surroundings…)

Other comments:
Appendix II

FMS-RS

Functional Mobility Scale – Rett syndrome

Adapted by

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With permission from

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- Telethon Kids Institute
  The University of Western Australia, Perth, Australia

INTRODUCTION

The Functional Mobility Scale (FMS-RS) has been constructed to describe walking ability on level ground in Rett syndrome by focusing on the level of assistance. It is modified from the original Functional Mobility Scale (FMS) developed by the Hugh Williamson Gait Laboratory.

The FMS-RS rates walking ability at 5, 50 and 500 metres (or 5, 50, 500 yards). This represents the walking ability in the home, at the day center (comprising pre-school, school, activity center) and in the community. The person with Rett syndrome might need different levels of assistance in different environments. The distances are a guide. It is the environment that is most relevant.

Assessment is based on questions asked of the parent/care-giver (not direct observation). The walking ability is rated at each distance according to level of assistance. The rating of level of assistance has been adapted from the Rett syndrome Gross Motor Scale developed by the Telethon Kids Institute. If the person uses orthotics regularly they should be included for the rating.

The FMS-RS is a performance measure. It is important to rate what the person actually does at this time point, not what they can do or used to be able to do.
RATING

Name:_________________________________ Date:_________________ Age:______________

Questions
Is your child/the person capable of walking 10 steps with/without support (including gait devices)?

If no, rate as 0
If yes, the following questions are asked

1) How much assistance* does your child/the person need to walk short distances in the house (for instance within her own room)? (5m)

2) How much assistance* does your child/the person need to walk in and between rooms/classes at the pre-school/school or activity center? (50m)

3) How much assistance* does your child/the person need to walk long distances such as at the shopping centre or to/from the nearest bus stop or grocery store? (500m)

<table>
<thead>
<tr>
<th>FMS-RS</th>
<th>Home Ambulation (indoors)</th>
<th>Day Center Ambulation (indoors/outdoors)</th>
<th>Community Ambulation (indoors/outdoors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 m</td>
<td></td>
<td></td>
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<tr>
<td>50 m</td>
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<td>500 m</td>
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<td></td>
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<tr>
<td>Level of assistance</td>
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</tr>
</tbody>
</table>

*Assistance:

0) Unable – caregiver transports person in stroller, wheelchair, wheeled seating system

1) Maximal support – support of trunk, caregiver assists steps (person might also need a walking aid)

2) Moderate support – two hand support or use of a gait device (for instance crutches, walker, walking frame)

3) Minimal support – one hand support

4) None - independent with/without supervision/verbal guidance (when applied to community ambulation the person might need a hand for safety reasons when walking in areas of busy traffic)

Does the person use a walking aid?: No ☐ Yes ☐ Please state which one:__________________
References


