Clinical and genetic correlations of scoliosis in Rett syndrome

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Abstract
Aim To identify the clinical features correlating with the presence and severity of scoliosis in girls with Rett syndrome (RTT).
Method Seventy-five girls with a clinical and genetically determined diagnosis of RTT participated in this cross-sectional study. Clinical scales administered included the Rett assessment rating scale, the modified Ashworth scale, the Rett syndrome motor evaluation scale, the PainAD, and the scale of evaluation of purposeful hand function. Multivariable analyses, such as ordinal logistic regression and ANCOVA, were used to assess the correlation between these scales and a clinical score of scoliosis.
Results About 60% of patients had scoliosis, in general mild or moderate. The severity of scoliosis correlated with age and important neurological factors such as muscular hypertonus and hyperreflexia, standing, walking (level walking and on stairs), and postural transitions. No association was found with global disease severity, hand function, pain, or type of genetic mutation.
Interpretation Scoliosis is a relevant problem in RTT. It should be carefully monitored along the life span, especially in conjunction with (loco-)motor impairment in these patients.

Keywords Rett syndrome · Scoliosis · Walking · Postural transitions · Motor function

Abbreviations
ANCOVA Analysis of covariance
ASA American statistical association
MAS Modified Ashworth scale
MBD Methyl-binding domain
NLS Nuclear localization signal
RARS Rett assessment rating scale
RESMES Rett syndrome motor evaluation scale

Introduction
Rett syndrome (RTT) is a neurodevelopmental disorder predominantly linked to MECP2 gene mutations, affecting one female birth in 10,000/15,000 [1]. Scoliosis is an associated condition of RTT, with a high clinical impact [2]. Complications related to neuromuscular scoliosis usually develop, such loss of sitting balance, deterioration of walking skills, progressive restrictive lung disease, and pain [3]. Almost half of RTT girls with classic mutations have scoliosis, and its prevalence increases to 85% at age of 16 years [4–7]. The average age of onset is 11 years [8] but can be earlier than 4 years, as reported in 28% of girls with RTT in one study [9]. Scoliosis in RTT is of neuromuscular origin, arises early, is rapid in progression, and it is not necessarily halted by the cessation of growth [10].

The scoliotic curves in RTT progress on average from 14 to 21° per year [7, 10, 11]. The prevalence of scoliosis (with curve > 39°) has been reported to be 27% in the age range...
6–9 years and 51% at age > 9 years [12]. Specific mutations in the MECP2 gene correlate with the presence of scoliosis. Girls with a T158M, R168X, or R255X mutation would be at higher risk than those with a R294X mutation [4]. A lower incidence of scoliosis has been reported in association with C-terminal mutations [8], but these mutations can be associated with kyphosis [13]. The p.Arg133Cys and p.Arg294X mutations correlate with later development of scoliosis, the p.Arg306Cys mutation is associated with non-progressive scoliosis, while the p.Arg168X, p.Arg255X, and R270X mutations are associated with early and severe scoliosis [14].

Anomalies and defects in the muscle tone of the paravertebral musculature have been hypothesized as underpinning the onset of scoliosis in RTT [15]. Pyramidal signs are associated with scoliosis [16]. Most studies found that preservation of walking and sitting would protect from the development of scoliosis [4, 8, 17, 18]. However, there is very poor information on the correlates between (loco-) motor symptoms and the presence and severity of scoliosis. Chronic pain is another symptom associated with scoliosis. However, in most studies, pain has not been evaluated with standardized scales, making it difficult to establish a clear correlation with scoliosis and its severity. Moreover, while there are studies that correlate the severity of scoliosis to the genetic mutation, there is still a knowledge gap concerning the association between the severity of scoliosis and clinical neurological aspects, including motor and manual function.

Our study aims to investigate the relationship between severity of scoliosis, motor function, and neurological aspects such as hypertonus in a large sample of girls with RTT. To this purpose, we conducted a cross-sectional study in which such functions have been clinically evaluated with formal and standardized scales.

Method

Participants

Girls coming from all Italian regions were evaluated in our clinic (IRCCS Fondazione Don Carlo Gnocchi, Milan). Parental contacts were provided by AIRETT (Italian Association Rett Syndrome). The objective of the assessment was to provide counseling to the family and to the hospitals where the girls were already in charge, with the aim of starting or improving a rehabilitation program. Patients were enrolled consecutively for a period of 3 years. No follow-up evaluation was possible. Two physicians with specific competence in pediatric neurology and rehabilitation examined scoliosis in 75 patients diagnosed with RTT (all females; mean age 11.1 (standard deviation, SD 8.9), range 3–40 years). Inclusion criteria for patients were: (i) diagnosis of typical RTT according to Neul et al. [19]; (ii) age ≥ 3 years; (iii) positive genetic test (in case of negative genetic test, participation in the study was allowed only after clinical re-evaluation for the verification of the diagnostic criteria); (iv) provision of written informed consent, provided by the parents or legal guardian(s). We excluded patients with encephalic damage secondary to perinatal trauma, neurometabolic disease, or cerebral infection. We also excluded patients with impairment of psychomotor development in the first 6 months of life or with a clinical/genetic picture compatible with a diagnosis of a variant of RTT. The study was approved by the local Ethical Committee (Approval Number 4_18062014).

Neurological and musculoskeletal assessment

All patients underwent a neurological examination, including a clinical evaluation of the musculoskeletal components of the limbs (reduction in the range of motion in the main articulations, the presence of heterometry of the lower limbs) and of the spine, as well as assessment of the osteotendinous reflexes in the four limbs. Postural examination of sitting balance and asymmetry in the sitting position was evaluated clinically.

Clinical scales

Scale of assessment of scoliosis. Since X-ray images were not standardized (patients could be supine, seated, or standing, depending on the degree of disease severity), the presence of scoliosis was assessed and coded on a 0–3 ordinal scale, which takes into account type and severity of impairment. This scale is in use for the clinical evaluation of scoliosis in cerebral palsy [20, 21]. The scoring system is 0: no scoliosis; 1: mild scoliosis, curve visible only on thorough examination in forward bending; 2: moderate scoliosis, obvious curve in both upright and forward bending; 3: severe scoliosis, pronounced curve preventing upright position without external support.

Rett Assessment Rating Scale (RARS). This scale [22], completed by parents, assesses all aspects of RTT to ascertain its clinical severity. There are seven subscales in RARS: (i) sensory function; (ii) cognitive function; (iii) motor structure and function; (iv) emotions; (v) autonomy; (vi) physical characteristics; (vii) behavioral characteristics. Each item is evaluated on a 7-point ordinal scale. Scores from 0 to 55 indicate mild impairment, 56–81 moderate impairment, and 82–124 severe impairment.

Modified Ashworth Scale (MAS). The modified version [23] was adopted to assess the degree of spasticity of the four limbs. This scale grades muscle spasticity in terms of response of muscle tone to passive stretching on a 0–5 ordinal scale: 0, normal muscle tone; 1, slight increase in muscle
tone, “catch” when limb moved; 2, more marked increase in muscle tone, but limb easily flexed; 3, considerable increase in muscle tone; 4, limb rigid in flexion or extension. Using this classification system, we assessed six loci (shoulder, elbow, wrist, hip, knee, and foot) and calculated a total score, which we interpreted in a descriptive sense only as a proxy for the level of spasticity.

Rett Syndrome Motor Evaluation Scale (RESMES). Motor function was assessed using RESMES [24, 25], which is composed of 25 items assessing motor performance across six dimensions: (i) standing; (ii) sitting; (iii) transitions; (iv) walking; (v) running; and (vi) walking up/downstairs. Each of the 25 items is scored on an ordinal scale (0–4 for 16 items; 0–2 for nine items); the overall score is a sum of the scores of these individual items. Regarding the multivariable analysis, an aggregated score was created for each of the six RESMES sections.

Scale of evaluation of purposeful hand function. This is a 1–8 ordinal scale [26], where score 1 indicates no observed hand function, and score 8 a well-structured ability to use the hand in different situations. Each hand is evaluated independently. We created a derived variable, attributing to each participant the score of the dominating hand; if no hand preference was reported/observed, the highest score was taken into consideration.

The PainAD scale. This scale [27] measures the concomitant presence of painful symptoms during assessment. It is composed of five items, each assessed using a 0–2 ordinal score: (i) breathing; (ii) negative vocalization; (iii) facial expression; (iv) body language; and (v) consolability. Total scores range from 0 to 19; a score above 3 indicates the presence of moderate-to-severe pain. This cutoff was used in the present evaluation to exclude concomitant acute pain.

**Statistical analyses**

Data were analyzed using descriptive statistics, such as mean and SD. A multiple regression model (ordinal logistic) was run, using degree of scoliosis as the dependent variable and age, total RARS scores, RESMES scores, Ashworth scores, pain scores, and purposeful hand functioning scores as covariates. To circumscribe possible multicollinearity issues (as multicollinearity could be related with problems of numerical instability and reliability of the estimates), the same model was repeated independently using the score of each of the six RESMES subsections. We also estimated an ANCOVA model in the analysis by genotype, inserting scoliosis scores as the dependent variable, domain of mutation as the independent variable, and age, total RESMES scores and total RARS scores as covariates. A nominal value of 0.05 was set to evaluate significance of each p-value, which were reported in agreement with the 2016 ASA statement [28].

**Clinical illustration**

In the Supplementary Materials, we describe two clinical cases, their scoliosis level, and their functioning; two illustrative video clips are also available.

**Results**

**Overview and descriptive analysis**

More than half of the females had scoliosis, generally mild (17 females, 22.6%) or moderate (25, 33.3%), with some severe (5, 6%). Twenty-eight females (37.3%) did not have scoliosis. The mean age of females with scoliosis was 14.5 (SD 9.08, range 4–40) years, while the mean age in those without scoliosis was 11.13 (SD 8.92, range 3–40) years. Table 1 shows (cross-sectionally) the distribution of scoliosis judgments, stratified by level of skeletal maturity (< 10 years; 10–18 years; > 18 years). In the subsample of girls aged < 10 years, 58% had no scoliosis, 42% of patients had scoliosis (21% mild, 21% moderate), while no patient within this age range was diagnosed with severe scoliosis.

| Scoliosis | N | % |
|-----------|---|---|
| < 10      | 25| 58|
| 10–18     | 19| 100|
| > 18      | 13| 100|

**Scoliosis.** 0: no scoliosis; 1: mild scoliosis, curve visible only on thorough examination in forward bending; 2: moderate scoliosis, obvious curve in both upright and forward bending; 3: severe scoliosis, pronounced curve preventing upright position without external support

| Age range | Scoliosis | N | % |
|-----------|-----------|---|---|
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| 10–18     | 19        | 100|
| > 18      | 13        | 100|

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We remark that scoliosis was mild-to-moderate in the large majority of the cases, and it was of severe entity in 16% of girls aged 10–18 years, and in 15% of girls aged > 18 years.

Table 2 outlines the performance on different evaluation scales, illustrating the degree of severity of scoliosis. We noticed that both Ashworth and RESMES scores increased with increasing severity of scoliosis. The severity of scoliosis increased with age, but the global severity of RTT (measured by RARS scores) seems comparable between girls without or with mild-to-moderate scoliosis.

Table 3 shows descriptive statistics by domain change location. Carboxy-terminal mutations seem to be associated with milder forms of RTT than nuclear localization signal (NLS) mutations, methyl-binding domain (MBD) mutations, or large deletions. NLS mutations and large deletions are also associated with more severe forms of scoliosis than other mutations.

### Multivariable analyses

We estimated ordinal logistic regression models, as described in the Method section, using the severity of scoliosis score as dependent variable. We firstly inserted age, the total RARS score, the hand functioning score, the pain score, and the total RESMES score as regressors. Results indicated a positive significant effect of age (β = 0.13 (0.03), t = 4.14, p < 0.0005) and of total RESMES scores (β = 0.04 (0.17), t = 2.32, p = 0.02). No other variable proved significant. When estimating the same model, but inserting Ashworth total scores instead of RESMES total scores. While not far from significance (F (7,63) = 1.66, p = 0.13), we did not detect a consistent association between the domain of mutation with scoliosis.

**Analysis by genotype**

For all females, we knew the type of mutation that was involved in the MECP2 gene. This was classified into the domain of mutation using a large genotyping resource (http://mecp2.chw.edu.au/). In our database, we estimated an ANCOVA model to verify whether the domain of mutation could be associated with severity of scoliosis in patients with RTT. The model was adjusted by age, RARS total scores, and RESMES total scores. While not far from significance (F (7,63) = 1.66, p = 0.13), we did not detect a consistent association between the domain of mutation with scoliosis.

The association was also not significant in the unadjusted model (F (7,66) = 1.08, p = 0.38).

### Table 2 Characteristics of the sample (n=75) by severity of scoliosis

| Scoliosis | N | Age | RARS | Pain | MAS | Hand R | Hand L | RESMES T | RESMES S |
|-----------|---|-----|------|------|-----|--------|--------|----------|----------|
| 0         | 28| 5.1 (4.9) | 64.5 (9.3) | 0.8 (1.5) | 4.0 (3.3) | 2.9 (2.2) | 2.6 (2.0) | 35.4 (14.8) | 1 (2);2 (3);3 (4);4 (8);5 (5);6 (1);7 (4);8 (1);9 (0) |
| 1         | 17| 12.3 (10.4) | 62.5 (7.5) | 0.4 (0.6) | 8.3 (7.2) | 2.2 (1.4) | 1.6 (1.2) | 36.7 (15.4) | 1 (0);2 (2);3 (3);4 (3);5 (5);6 (1);7 (3);8 (0);9 (0) |
| 2         | 25| 16.3 (8.7) | 65.4 (7.9) | 1.1 (1.4) | 13.9 (9.6) | 2.8 (2.2) | 2.8 (2.1) | 43.5 (17.8) | 1 (1);2 (1);3 (2);4 (2);5 (8);6 (4);7 (5);8 (2);9 (0) |
| 3         | 5 | 18.3 (5.6) | 72.8 (10.6) | 0.6 (1.3) | 20.4 (17.5) | 2.2 (1.3) | 1.2 (0.4) | 53 (31)  | 1 (1);2 (0);3 (0);4 (5);5 (1);6 (0);7(1);8 (0);9 (2) |

We report information on age and performance (mean (standard deviation)) in the RARS, PainAD, MAS, hand function, and RESMES scales. **Scoliosis.** 0: no scoliosis; 1: mild scoliosis, curve visible only on thorough examination in forward bending; 2: moderate scoliosis, obvious curve in both upright and forward bending; 3: severe scoliosis, pronounced curve preventing upright position without external support. **RARS:** RARS total score; **Pain:** PainAD total score; **MAS:** Ashworth total score (sum of six districts separately evaluated on the left/right); **Hand R:** score on the hand function scale (right); **Hand L:** score on the hand function scale (left); **RESMES T:** Total RESMES scores; **RESMES S:** RESMES stanine score (number of girls). Raw scores below 17 (stanine 1 or 2) indicate no or minimal deficit. Stanine values 1–2; 3–4; 5–6; 7–9 would correspond, respectively, to a level of minimal (or null), mild, moderate, and severe impairment. MAS, modified Ashworth scale; RARS, Rett assessment rating scale; RESMES, Rett syndrome motor evaluation scale.
Scoliosis in RTT is a common and relevant problem. Spinal deformities can start at a very young age [9] and may progress to severe forms that require surgical management [2, 4, 5, 7, 8]. In particular, the precocity of measurable scoliosis in RTT was reported by Hennessy et al. [29], who observed early signs of scoliosis from 2 years and 9 months of age. Percy et al. [4], in a large series of girls with RTT, reported the presence of scoliosis in about 40% of the patients aged 1–4 years. Killian et al. [9] found cases of scoliosis (Cobb’s angle < 40°) in four out of 27 girls aged less than 1 year; 21 out of 159 girls aged less than 3 years; 58 out of 253 girls aged less than 4 years plus one case with Cobb’s angle > 40°. These findings justify the inclusion of girls aged 3+ in our sample.

The data presented indicate that age is significantly associated with the degree of scoliosis, i.e., older girls are likely to have more severe scoliosis. We highlight that 42% of the subsample of < 10 years old girls had early onset scoliosis (i.e., a score of 1 to 3). In the literature, early signs of scoliosis have been described before 4 years [9] or 3.9 years [8]. In our case, we did not find scoliosis in the girls examined at 3 years (n = 13), while the age range for girls with scoliosis started at 4 years of age. For the 10–18 and > 18 age ranges, the prevalence was 90% and 92%, respectively. It is also worth observing that only 16% of girls aged 10–18 and 15% of girls aged > 18 was diagnosed with severe scoliosis. How - ever, this result was not far from the threshold of statistical significance.

Discussion

Scoliosis is a common and relevant problem in RTT. Spinal deformities can start at a very young age [9] and may progress to severe forms that require surgical management [2, 4, 5, 7, 8]. In particular, the precocity of measurable scoliosis in RTT was reported by Hennessy et al. [29], who observed early signs of scoliosis from 2 years and 9 months of age. Percy et al. [4], in a large series of girls with RTT, reported the presence of scoliosis in about 40% of the patients aged 1–4 years. Killian et al. [9] found cases of scoliosis (Cobb’s angle < 40°) in four out of 27 girls aged less than 1 year; 21 out of 159 girls aged less than 3 years; 58 out of 253 girls aged less than 4 years plus one case with Cobb’s angle > 40°. These findings justify the inclusion of girls aged 3+ in our sample.

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Table 3  Characteristics of the sample (n = 75) by domain change location

| Domain | N | Age | Scoliosis | RARS | Pain | MAS | Hand R | Hand L | RESMES T | RESMES S |
|--------|---|-----|---------|------|------|-----|-------|-------|---------|---------|
| N-term | 1 | 4   | 0 (1);1 (0); 2 (0);3 (0) | 73   | 0    | 0   | 1     | 1     | 55.5    | 7       |
| MBD    | 21| 10.1 (7.6) | 0 (6);1 (8); 2 (6);3 (1) | 64.2 (8.4) | 0.9 (1.5) | 8.1 (5.7) | 2.1 (1.5) | 2.0 (1.4) | 38.6 (14.7) | 5       |
| Int    | 5 | 10.6 (13.6) | 0 (3);1 (1); 2 (1);3 (0) | 59.9 (6.7) | 0 (0) | 4.4 (3.6) | 3.8 (3.4) | 3.6 (3.2) | 45 (23.5) | 5       |
| TRD    | 12| 10.6 (9.3) | 0 (7);1 (0); 2 (4);3 (1) | 65.9 (8.3) | 0.6 (1.2) | 7.1 (9.7) | 3.1 (1.9) | 2.2 (1.7) | 41.1 (21.3) | 5       |
| NLS    | 7 | 12.9 (9.2) | 0 (1);1 (1); 2 (4);3 (1) | 68.9 (6.2) | 1.7 (2.2) | 10.7 (9.3) | 2 (1.4) | 1.1 (0.4) | 46.3 (14.9) | 6       |
| C-term | 9 | 14 (12.1) | 0 (4);1 (2); 2 (3);3 (0) | 63.6 (9.9) | 0.3 (0.5) | 14.8 (10.7) | 3.67 (2.2) | 4.0 (1.8) | 29.6 (14.0) | 4       |
| Del    | 15| 10.8 (7.6) | 0 (3);1 (5); 2 (6);3 (1) | 64.8 (9.9) | 0.9 (1.1) | 13.4 (12.8) | 2.1 (1.9) | 2.4 (2.0) | 43.1 (20.6) | 5       |
| Other  | 5 | 12 (9.5) | 0 (2);1 (1); 2 (1);3 (1) | 66.1 (11.1) | 0.4 (0.5) | 3.6 (2.7) | 4.4 (1.1) | 2.4 (2.1) | 29.7 (14.8) | 4       |

We report information on age, scoliosis, and performance (mean (standard deviation)) in the RARS, PainAD, MAS, scale of purposeful hand function, and RESMES scales.

N-term: amino-terminal; MBD: methyl-binding domain; Int: inter-domain region; TRD: transcription repression domain; NLS: nuclear localization signal; C-term: carboxy-terminal; Del: large deletion. Scoliosis: 0: no scoliosis; 1: mild scoliosis, curve visible only on thorough examination in forward bending; 2: moderate scoliosis, obvious curve in both upright and forward bending; 3: severe scoliosis, pronounced curve preventing upright position without external support. RARS: RARS total score; Pain: PainAD total score; Ash: Ashworth total score (sum of six districts separately evaluated on the left/right); Hand: score on the hand function scale (right); Hand: score on the hand function scale (left); RESMES: Total RESMES scores; RESMES: Average RESMES stanine score. Raw scores below 17 (stanine 1 or 2) indicate no or minimal deficit. Stanine values 1–2; 3–4; 5–6; 7–9 would correspond, respectively, to a level of minimal (or null), mild, moderate, and severe impairment. MAS, modified Ashworth scale; RARS, Rett assessment rating scale; RESMES, Rett syndrome motor evaluation scale.
significance, and our negative finding could be attributed to the fact that the sample size was relatively small for genetic investigations.

The degree of spasticity (MAS score) correlated with the severity of spinal deformities. This correlation was previously reported by Hanks [16], possibly confirming the neuromuscular origin of this type of scoliosis. Greater severity of scoliosis and faster progression has been associated with hypotonia and muscular weakness [10]. However, a recent study did not report a correlation between alterations in muscle tone and scoliosis [9]. It should be noted that we systematically evaluated six joint loci with MAS which, at least to our knowledge, has not been done by previous studies.

Results from ordinal logistic regression models showed that the magnitude of scoliosis was associated with the severity of (loco-)motor symptoms measured with the RESMES scale, but not with the general severity of the disease (RARS). In particular, independent walking (level walking and on stairs) and postural transition significantly correlated with the presence and severity of scoliosis. In the literature, independent walking and sitting was shown to be related to a lower risk of severe spinal deformities [4, 8, 9]. Recent studies conducted on large samples of patients also highlighted a correlation between walking capacity and the evolution of scoliosis [8, 9, 30]. Our data are in agreement with this general picture, and support the assumption that impaired walking and poor stair negotiation are associated with scoliosis in RTT. In our study, sitting and running did not show a significant correlation with scoliosis. Regarding sitting, the RESMES scale evaluates multiple aspects of this motor task, i.e., sitting on a stool with or without feet support or sitting on the floor, and results might therefore differ from the simple clinical observation of the absence of sitting balance [9]. As to running, this may depend on the very low number (n = 3, 4%) of girls able to run (floor effect). Transitions evaluated with the RESMES also emerged as important correlates of scoliosis. This result is very important from a clinical and rehabilitative point of view. Great effort should be given to maintain walking, walking upstairs and downstairs, and postural transitions, albeit with assistance, in girls with RTT. These are practices commonly used in rehabilitation and important for families [31]. In particular, going up and down the stairs alternately activates the trunk muscles, contributing to improved flexibility of paravertebral muscles.

We did not find an association between hand use and the risk of spinal deformities. This is in line with the study of Downs and coll [8] but in contrast to other reports [4, 9, 32]. These discrepancies may also result from the lack of longitudinal data in our study. Girls with poor functional hand use might develop scoliosis at later stages. An important question to address is whether scoliosis in these girls may progress before or after menarche, or at later stages of adolescence. This is open for future longitudinal research.

Pain is another factor of RTT investigated in the literature, but whose role seems uncertain with respect to spinal deformities. Such uncertainty also follows from the fact that informal and non-standardized pain assessment has been reported by previous investigations [21]. In our study, we adopted a formal scale (i.e., PainAD) to measure pain in these girls and found no correlation of pain with severity of scoliosis. Still, PainAD only captures an acute component of pain, whereas scoliosis could correlate with chronic pain that should be tested with specific scales [33]. In this regard, a deranged sensitivity to pain in RTT has been described [34]. This issue remains open for future research.

The main strength of our study is that unlike previous investigations, structured and standardized scales were adopted to measure the neurological and physical function of our patients; however, Cobb’s angles were not available, and the degree of scoliosis was assessed only with a validated clinical scale. Following these results, we plan to conduct a large study that also measures Cobb’s angle, skeletal maturity, and Risser sign. Another limitation is the lack of longitudinal evaluations, preventing a clear identification of factors predicting the onset of scoliosis in girls with RTT.

In conclusion, our cross-sectional study investigated the main clinical factors associated with scoliosis in RTT. We found that age, impaired upright standing, postural transitions, and walking, as well as hypertonus, were associated with the severity of scoliosis. This suggests the importance of periodic clinical and radiological evaluation from the very early detection of postural asymmetries. Furthermore, postural transitions and walking upstairs and downstairs should be encouraged in the rehabilitation protocols of girls with RTT, to help limit the impact and progression of spinal deformities. Our results also suggest the possibility of using the RESMES scale as a clinical tool to comprehensively evaluate and monitor (loco-)motor function in girls with RTT, as it was shown to highly correlate with the presence and severity of scoliosis. The relevance of this funding is that the RESMES scale can be performed by caregivers in a home environment [24], allowing close monitoring of the (loco-)motor impairments of girls with RTT and an early rehabilitative intervention.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00586-022-07217-8.

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Declarations

Conflicts of interest The authors declare that they have no competing interests.

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