

Quantification of functional abilities in Rett syndrome: a comparison between stages III and IV

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Abstract: We aimed to evaluate the functional abilities of persons with Rett syndrome (RTT) in stages III and IV. The group consisted of 60 females who had been diagnosed with RTT: 38 in stage III, mean age (years) of 9.14, with a standard deviation of 5.84 (minimum 2.2/maximum 26.4); and 22 in stage IV, mean age of 12.45, with a standard deviation of 6.17 (minimum 5.3/maximum 26.9). The evaluation was made using the Pediatric Evaluation of Disability Inventory, which has 197 items in the areas of self-care, mobility, and social function. The results showed that in the area of self-care, stage III and stage IV RTT persons had a level of 24.12 and 18.36 ($P=0.002$), respectively. In the area of mobility, stage III had 37.22 and stage IV had 14.64 ($P<0.001$), while in the area of social function, stage III had 17.72 and stage IV had 12.14 ($P=0.016$). In conclusion, although persons with stage III RTT have better functional abilities when compared with stage IV, the areas of mobility, self-care, and social function are quite affected, which shows a great functional dependency and need for help in basic activities of daily life.

Keywords: Rett syndrome, disability evaluation, self-care, mobility limitation

Introduction

Rett syndrome (RTT) is a chronic and incapacitating condition that has distinct phenotypic characteristics. It is a neurological disorder characterized by cognitive impairments, communicative dysfunctions, stereotyped movements, and changes in growth.^{1,2} Its genetic identification was described in 1999 as an alteration in the *MECP2* gene,³ but the first characterization was established in 1966 by the Austrian physician Andreas Rett,⁴ who reported observations of girls who demonstrated autistic behavior, dementia, apraxia of gait, stereotypic hand movements, and loss of facial expression.^{5,6} The diagnosis of RTT is based on clinical criteria⁷ established by Hagberg et al⁸ and subsequently updated by Hagberg et al⁹ and reviewed by Neul et al.¹⁰

RTT almost exclusively affects girls,¹¹ who show no abnormalities at birth or in the first months of life. However, between 6 and 18 months of age, RTT sufferers display regression of developmental milestones, irritability, and stagnation in neuromotor development.^{12,13} Other characteristic problems include a loss of functional abilities, with symptoms of seizures,^{14–16} characteristics of autism, and autonomic dysfunction¹⁷ with the prognosis of severe cognitive impairment.¹⁸

The characteristic clinical pattern and profile of RTT over time was illustrated in the system of four clinical stages.¹⁹ This system still remains useful for the description of the classical form of the disease:²⁰ stage I (stagnation) – early onset stagnation stage at 6 months to 1.5 years, which includes developmental arrest, decelerating

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head growth, reduced communication and eye contact, and diminishing interest in play; stage II (regression) – the rapid destructive stage, at 1 year to 3 years with developmental deterioration, autistic features and stereotypies, severe dementia with loss of speech, and loss of hand skills with frequent hand wringing; stage III (pseudo-stationary stage) – contains some stabilization at preschool to school years, but exhibits gait ataxia, stereotypic hand movements, severe mental retardation or dementia, and epileptic seizures, and; stage IV (late motor deterioration) – the girls have decreased mobility around the age of 15 years and are often wheelchair-bound with persistent growth retardation. Scoliosis is also very common, emotional contact tends to be improved, and epilepsy becomes less common and more easily controlled.²⁰

Although the characteristics of the four stages of RTT are well presented and documented,^{19,20} a comparison between functional stages using an evaluation system that measures different functional areas is important for the understanding of capabilities in different everyday activities and also for monitoring disease progression. Due to the difficulty of early diagnosis and rapid passage through stages I and II^{7,9,10} it is difficult to collect data in the early stages of the disease. However, the later stages (III and IV) persist for several years and enable scientific study.

For professionals in rehabilitation, RTT is a particularly challenging condition with respect to the severity of motor and cognitive impairment, the osteotendinous retractions, and progressive immobility, which characterize the later stages of the disease. In addition to professionals and family members, society needs information about the capabilities of people with RTT and the changes that occur at different stages. Lim et al²¹ conducted a qualitative study exploring the daily experiences of families caring for children with RTT and found participants reporting a lack of education and rehabilitation and support services available to them. Those families reported that limited access to information reduced families' capacity to adequately meet the needs of their child.

An interesting factor to assist in clinical practice is the development of studies that quantify the abilities of persons with RTT, which enables the verification of the true extent of capacities that will help to inform families, community, and appropriate interventions. It is important to present key information for clinicians and families regarding possible skill areas that may guide therapeutic interventions.²²

To date, a growing number of studies have revealed a variety of RTT characteristics including pathogenetical mechanisms,^{23–26} physiological characteristics,²⁷ polysomnographic abnormalities,²⁸ microvascular abnormalities,²⁹ seizures,^{30,31}

bone abnormalities,^{32–35} oxidative stress,³⁶ and nutritional factors.^{37,38} However, considering the importance of functionality, few studies have aimed to quantify the different functional abilities of RTT persons. Larsson et al³⁹ made a description of early development; Downs et al⁴⁰ used observations for hand function; Baptista et al⁴¹ as well as Djukic and McDermott⁴² examined the pattern of visual fixation and social preferences using eyetracking technology. Marschik et al^{43,44} delineated the achievement of early speech-language milestones in RTT. Lotan et al⁴⁵ investigated a physical exercise program with a treadmill in RTT in order to improve functional skills, and Foley et al²² used video data to investigate the course of gross motor function in girls and women with RTT. Finally, Lane et al⁴⁶ described the impact of clinical severity on quality of life among female children and adolescents with classic RTT and found that quality of life is significantly related to clinical severity, as they also examined the relationships among *MECP2* mutations, clinical severity, and psychosocial and physical aspects of quality of life for persons with RTT.

Furthermore, improved understanding on the motor and cognitive capacity of RTT is particularly important for professionals in rehabilitation, in view of the impact of RTT on the level of functional independence of these persons.

Therefore, in order to provide detailed knowledge of the functional abilities of people with RTT, in the current study we aimed to characterize and identify areas of greater functional abilities and verify functional differences between persons at stages III and IV of RTT.

Methods

This study was approved by the ethics committee for review of research projects of the Hospital of Clinics of the School of Medicine of the University of São Paulo under protocol number 1033/03 and informed consent was obtained from the parents of the persons with RTT.

Participants

We evaluated 60 persons with RTT, who met the criteria for classic or typical form of the disease; 38 persons were in stage III, mean age (years) of 9.14 with a standard deviation of 5.84 (minimum 2.2/maximum 26.4) and 22 persons were in stage IV, mean age of 12.45 with a standard deviation of 6.17 (minimum 5.3/maximum 26.9). These stages were chosen for evaluation because early stages of the disease (stage I and II) persist briefly with rapid progression, making them particularly difficult to monitor and diagnose.

The participants were a consecutive selection of persons with RTT, consisting of a convenience sample determined

by availability. Parental permission to conduct the study was obtained from every parent by signing a consent form. Participant's parents needed to be available to answer the necessary items with the simultaneous presence of their children.

Of the 60 classifications and evaluations, 40 (67%) were performed at the outpatient clinic of the pediatric neurology department of the University of São Paulo and 20 (33%) were performed at the Brazilian Rett Syndrome Association. The diagnosis and classifications as used by Larsson et al⁴⁷ and Halbach et al⁴⁸ were made by a group of child neurologists of the participating institutions with experience in RTT, and who had been following the clinical treatments and therapeutic interventions of most of the participants for several years.

Instrument

The Pediatric Evaluation of Disability Inventory (PEDI) was used to verify functional difficulties. The PEDI was developed by Haley et al⁴⁹ and translated, validated, and adapted to address the specificities of the sociocultural environment in Brazil, by Mancini,⁵⁰ with permission and collaboration of the authors of the original assessment. Psychometric properties of the PEDI (Brazilian version) suggested high inter-interviewer reliability (intraclass correlation coefficient: 0.91 to 0.99) and excellent intrarater reliability (Pearson's correlation: 0.89 to 0.98)⁵⁰ and it was used in several earlier studies.⁵¹⁻⁵⁴

The main purpose of this assessment instrument is to collect information about capacity and performance in the areas of self-care, mobility, and social function. The age at which more than 90% of children were able to perform a particular activity is determined and validated. It is expected that over 90% of typical developing children are able to perform all activities of the PEDI after 8 years of age.

Procedures

To investigate functional abilities, 73 self-care, 59 mobility, and 65 social function activities (total of 197) were assessed, for which the person was considered able (1) or unable (0) to perform the activity. For administering the PEDI, prior minimal training, as recommended by the authors,⁴⁹ was conducted. Although the PEDI can be applied without the presence of the person, this study employed the method of interviewing the parents concurrent to direct observation of all persons with RTT.

All interviews were held in the assessment room of the participating institutions. Most interviews were conducted with the presence of the mother of the participants (n=54;

90%) or with the father and mother together (n=5; 10%). In the case of disagreement (only in a few occasions) agreement by discussion among parents and the evaluator was necessary to score a response.

Data analysis

The results of functional abilities were assessed by transforming the raw score into a continuous score as used by Öhrvall et al.⁵⁵ This continuous score data allows the use of the PEDI data for people under and over the age of 8 years. In addition, using the continuous score made it possible to perform comparisons between the areas of self-care, mobility, and social function of the PEDI functional skills that feature a number of different activities.

To present capacity using the PEDI items to compare stage III and IV, values were weighted and organized according to age. An item was not considered valid if the person had not reached the age where certain functional abilities can be performed by at least 90% of children without any changes. For this reason, the number of items considered valid differed between children younger and children older than 8 years old.

Statistical analysis

Descriptive statistics were used to assess the sample characteristics. A two-way repeated measures analysis of variance (ANOVA) was used to compare the scores obtained in the areas of mobility, self-care, and social function on each stage of RTT. By this means, the different areas (mobility, self-care, social function) were taken as within factor and the two stages (stage III and stage IV) were taken as between factor. Finally, the one-way ANOVA was used to compare the stages of RTT on each area of the PEDI. Effect sizes were calculated by dividing the mean change scores for each stage in all areas of the PEDI by the standard deviation of continuous scores. The interpretation of effect sizes are based on Cohen's criteria, whereby an effect of less than 0.4 is considered small, 0.5 is considered moderate, and above 0.8 is considered large,⁵⁶ as used by Lin et al⁵⁷ and Tellegen and Sanders.⁵⁸ The SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) was used for data management and statistical analysis. Significance level was set at 0.05.

Results

The results of functional skills are presented through tables with presentation of functional skills that were executed by at least one of the persons with RTT, together with the age

at which 90% of normal children are expected to be able to accomplish the task. Also appearing in these tables are the numbers of persons where the activity was not applicable due to age and the number and percentage of persons with stage III and IV RTT able and unable to perform the task.

Self-care

For the PEDI assessment of the 73 activities that make up the area of self-care, 52 (71.2%) were not performed by any of the persons, who had reached the age to do so. The worst performance in this area was zero and the best 19, with a mean score of 6.67 ± 3.88 . This value corresponds to only 9.1% of possible performance. The three functional activities that were more often achieved considering both stages were as follows. First: eats foods whipped/mashed/strained, 60 individuals – 38 (100%) stage III and 22 (100%) stage IV. Second: eats foods ground/granulated, 36 (95%) stage III and 19 (87%) stage IV. Third: for stage III, eats foods chopped/in pieces and eats foods of various textures, 45 individuals (75%); and for stage IV allows nose to be wiped, 14 individuals (64%). Thus, we can see that most of those functional activities are in the food texture subarea. The results of all functional tasks from the self-care assessment are presented in Table 1.

Mobility

Eight of the 59 mobility activities (13.5%) evaluated were not performed by any person, despite the fact that they had reached the age to do so. The mean value of the raw score of mobility was 17.5 ± 15.1 , ranging from 1 to 44. This value corresponds to 30% of possible performance. The three functional activities that were more often achieved were as follows. First: sits if supported by equipment, 38 (100%) stage III and 22 (100%) stage IV. Second: sits in chair or bench unsupported, 35 (97%) stage III and 14 (64%) stage IV. Third: for stage III, moves within a room, but with difficulty, 34 (90%); and for stage IV, raises to sitting position in bed, eight (36%). The results of all functional mobility tasks are shown in Table 2.

Social function

Of the 65 social function activities evaluated, 50 (76.9%) were not performed by any of the participants despite them reaching the age at which the average population would normally do so. The mean raw score of social function was 3.4 ± 3.2 , ranging from 0 to 14. This value corresponds to 5.2% of possible performance. The three functional activities that were achieved more often were as follows. First:

Table 1 Self-care activities performed by at least one person with Rett syndrome

Able stage		Unable stage		Not applied n*	N**	Acquisition >90%, age range in years***	Activity****
III	IV	III	IV				
n (%)	n (%)	n (%)	n (%)				
38 (100)	22 (100)	0 (0)	0 (0)	–	1	0.6–0.11	Eats foods whipped/mashed/strained
36 (95)	19 (87)	2 (5)	3 (13)	–	2	1.0–1.5	Eats foods ground/granulated
32 (97)	13 (60)	1 (3)	9 (40)	5	3	3.0–3.5	Eats foods chopped/in pieces
32 (97)	11 (50)	1 (3)	11 (50)	5	4	3.0–3.5	Eats foods of various textures
29 (80)	14 (64)	7 (20)	8 (36)	2	24	2.0–2.5	Allows nose to be wiped
29 (76)	9 (41)	9 (24)	13 (59)	–	20	1.5–1.11	Keeps head still while hair is combed
13 (34)	1 (5)	25 (66)	21 (95)	–	10	0.6–0.11	Holds feeding bottle or glass with spout or straw
13 (34)	1 (5)	25 (66)	21 (95)	–	5	0.6–0.11	Feeds with fingers
12 (32)	11 (50)	26 (68)	11 (50)	–	15	1.6–1.11	Opens mouth for tooth brushing
8 (21)	0 (0)	30 (79)	22 (100)	–	11	1.0–1.5	Raises glass to drink, but may spill
8 (21)	0 (0)	30 (79)	22 (100)	–	29	1.0–1.5	Keeps hands elevated to be washed
8 (23)	0 (0)	27 (77)	22 (100)	3	64	2.6–2.11	Indicates when wetting diaper or pants – urinary control
7 (20)	1 (5)	28 (80)	21 (95)	3	70	2.6–2.11	Occasionally expresses desire to go to the bathroom (during the day)
7 (18)	0 (0)	31 (82)	22 (100)	–	39	1.0–1.5	Aids in pushing arms into shirt sleeves to dress
6 (16)	0 (0)	32 (84)	22 (100)	–	49	1.6–1.11	Aids in putting legs into pants to dress
4 (11)	3 (13)	31 (89)	19 (87)	3	69	2.6–2.11	Indicates need to be changed – bowel management
3 (9)	1 (5)	30 (91)	21 (95)	5	71	3.0–3.5	Constantly indicates need to evacuate in time to use the bathroom
3 (8)	0 (0)	35 (92)	22 (100)	–	6	1.6–1.11	Handles food with a spoon and raises to mouth
3 (8)	0 (0)	35 (92)	22 (100)	–	21	1.0–1.5	Raises comb or brush to hair
2 (6)	0 (0)	33 (94)	22 (100)	3	65	2.6–2.11	Occasionally indicates need to urinate (during the day)
2 (6)	0 (0)	34 (94)	22 (100)	2	12	2.0–2.5	Firmly raises glass without lid using both hands

Notes: *Number of children without adequate age to perform the activity; **activity number appearing on the Pediatric Evaluation of Disability Inventory evaluation form; ***age range in years at which more than 90% of the typically developing children acquired this activity; ****the items are sorted in order of decreasing capacity and identified by the number of persons in stage III and IV able to perform the activity.

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Table 2 Mobility activities performed by at least one person with Rett syndrome

Able stage		Unable stage		Not applied n*	N**	Acquisition >90%, age range in years***	Activity****
III	IV	III	IV				
n (%)	n (%)	n (%)	n (%)				
38 (100)	22 (100)	0 (0)	0 (0)	–	6	1.5–1.11	Sits if supported by equipment or adult (wheelchair)
34 (97)	14 (64)	1 (3)	8 (36)	3	7	2.6–2.11	Sits in chair or bench unsupported
34 (90)	4 (18)	4 (10)	18 (81)	–	28	1.0–1.5	Moves within a room, but with difficulty (fall; slow speed for age)
32 (84)	2 (9)	6 (16)	20 (91)	–	30	1.0–1.5	Moves between rooms, but with difficulty (fall; slow speed for age)
31 (82)	8 (36)	7 (18)	14 (34)	–	16	1.0–1.5	Raises to sitting position in bed or crib
31 (82)	3 (14)	7 (18)	19 (86)	–	38	1.6–1.11	Walks, but holds onto objects, adults, or support apparatus
31 (82)	2 (9)	7 (18)	20 (91)	–	26	1.0–1.5	Walks, but holds onto furniture, walls, or adults, or uses support apparatus
31 (82)	0 (0)	7 (18)	22 (100)	–	40	1.6–1.11	Moves 3–15 m (1–5 car lengths)
30 (79)	0 (0)	8 (21)	22 (100)	–	42	1.6–1.11	Moves 30–45 m (10–15 car lengths)
30 (79)	0 (0)	8 (21)	22 (100)	–	33	1.0–1.5	Changes physical location purposely
30 (79)	0 (0)	8 (21)	22 (100)	–	41	1.6–1.11	Moves 15–30 m (5–10 car lengths)
29 (76)	7 (32)	9 (24)	15 (68)	–	25	0.6–0.11	Rolls, scoots, drags, or crawls on floor
29 (76)	0 (0)	9 (24)	22 (100)	–	27	1.6–1.11	Walks without support – indoor
29 (76)	0 (0)	9 (24)	22 (100)	–	39	1.6–1.11	Walks unsupported – outdoor
29 (76)	0 (0)	9 (24)	22 (100)	–	43	1.6–1.11	Moves 45 m or more, but with difficulty (stumbles; slow speed for age)
29 (76)	0 (0)	9 (24)	22 (100)	–	45	1.6–1.11	Moves on level surfaces (flat sidewalks and streets)
26 (79)	4 (18)	7 (21)	18 (81)	5	17	2.0–2.5	Sits at edge of bed; lies down from sitting on edge of bed
25 (76)	0 (0)	8 (24)	22 (100)	5	46	2.0–2.5	Moves on slightly uneven surface (cracked asphalt)
25 (66)	0 (0)	13 (34)	22 (100)	–	20	1.6–1.11	Enters shower stall/tub
25 (66)	0 (0)	13 (34)	22 (100)	–	21	1.6–1.11	Exits shower stall/tub
23 (60)	0 (0)	15 (40)	22 (100)	–	29	1.0–1.5	Walks within a room without difficulty
23 (60)	0 (0)	15 (40)	22 (100)	–	47	1.6–1.11	Moves on irregular and uneven surfaces (lawns, gravel)
21 (60)	0 (0)	14 (40)	22 (100)	3	8	2.0–2.5	Sits and rises from chair or low/infant furniture
21 (60)	0 (0)	14 (40)	22 (100)	3	18	2.6–2.11	Gets in and out of own bed
21 (55)	0 (0)	17 (45)	22 (100)	–	44	1.6–1.11	Moves 45 m or more without difficulty
20 (57)	0 (0)	15 (43)	22 (100)	3	9	2.6–2.11	Sits and rises from adult-sized chair/wheelchair
20 (53)	0 (0)	18 (47)	22 (100)	–	48	1.6–1.11	Goes up and down ramps or inclines
19 (50)	0 (0)	19 (50)	22 (100)	–	31	1.6–1.11	Moves between rooms without difficulty
16 (42)	0 (0)	22 (58)	22 (100)	–	11	1.0–1.5	Moves in car; scoots on seat and in and out of car seat
15 (65)	0 (0)	8 (35)	22 (100)	21	10	6.0–6.5	Sits and rises from a chair without using arms
15 (39)	0 (0)	23 (61)	22 (100)	–	49	1.6–1.11	Moves up and down curbs
14 (42)	4 (18)	19 (58)	18 (81)	5	1	2.0–2.5	Sits if supported by equipment or adult (bathroom)
14 (42)	3 (14)	19 (58)	19 (86)	5	2	3.0–3.5	Sits unsupported on toilet or potty chair
14 (42)	0 (0)	19 (58)	22 (100)	5	12	3.0–3.5	Gets in and out of car with little aid or instruction
12 (46)	0 (0)	14 (54)	22 (100)	–	19	5.0–5.5	Gets in and out from own bed without using own arms
12 (34)	0 (0)	23 (66)	22 (100)	3	52	2.6–2.11	Walks up partial flight of stairs (erect)
10 (30)	0 (0)	23 (70)	22 (100)	5	4	3.0–3.5	Gets on and off from own adult-sized toilet
10 (29)	0 (0)	25 (71)	22 (100)	3	53	2.6–2.11	Walks up full flight of stairs, but with difficulty (slow for age)
8 (23)	0 (0)	27 (77)	22 (100)	3	3	2.6–2.11	Gets on and off from low toilet or potty chair
7 (18)	0 (0)	31 (82)	22 (100)	–	34	1.0–1.5	Moves concomitantly with objects on floor
7 (18)	0 (0)	31 (82)	22 (100)	–	34	1.0–1.5	Scoots or crawls up partial flight of stairs (1–11 steps)
7 (18)	0 (0)	31 (82)	22 (100)	–	51	1.6–1.11	Scoots or crawls up a complete flight of stairs (12–15 steps)
6 (32)	0 (0)	13 (68)	22 (100)	26	5	7.0–7.11	Gets on and off from toilet without using own arms
6 (16)	0 (0)	32 (84)	22 (100)	–	35	1.0–1.5	Carries objects small enough to hold in one hand

(Continued)

Table 2 (Continued)

Able stage		Unable stage		Not applied n*	N**	Acquisition >90%, age range in years***	Activity****
III	IV	III	IV				
n (%)	n (%)	n (%)	n (%)				
6 (16)	0 (0)	32 (84)	22 (100)	–	55	1.6–1.11	Scoots or crawls down partial flight of stairs (1–11 steps)
5 (13)	0 (0)	33 (87)	22 (100)	–	56	1.6–1.11	Scoots or crawls down a flight of stairs (12–15 steps)
4 (11)	0 (0)	31 (89)	22 (100)	3	58	2.6–2.11	Walks down full flight, but with difficulty (slow for age)
3 (9)	0 (0)	32 (91)	22 (100)	3	32	2.6–2.11	Moves indoors 15 m; opens and closes internal and external doors
3 (9)	0 (0)	32 (91)	22 (100)	3	57	2.6–2.11	Walks down complete flight of stairs (erect) (12–15 steps)
3 (8)	0 (0)	35 (92)	22 (100)	–	36	1.6–1.11	Carries large objects needing both hands
2 (8)	0 (0)	24 (92)	22 (100)	12	13	4.6–4.11	Gets in and out of car without aid or instruction

Notes: *Number of children without adequate age to perform the activity; **activity number appearing on the Pediatric Evaluation of Disability Inventory evaluation form; ***age range in years at which more than 90% of the typically developing children acquired this activity; ****the items are sorted in order of decreasing capacity and identified by the number of persons in stage III and IV able to perform the activity.

orients to sound, 38 (100%) stage III and 22 (100%) stage IV. Second: shows awareness and interest in others, 21 (55%) stage III and six (27%) stage IV. Third: recognizes own name or name of familiar person, 18 (47%) stage III and six (27%) stage IV. The results of all social functional tasks are presented in Table 3.

Comparisons between the areas of self-care, mobility, and social function

The repeated measures ANOVA showed a significant main effect of the areas on the PEDI score ($F_{2,116}=43.20$, $P<0.001$, partial $\eta^2=0.43$) and a significant areas by stage interaction effect ($F_{2,116}=33.75$, $P<0.001$, partial $\eta^2=0.37$). Differences in scores between areas are noted ($P<0.05$) when areas are compared in stage III, but in stage IV there was no difference between the areas of mobility and social function (Table 4).

To present the comparisons between the areas of self-care, mobility, and social function with stages III and IV of the disease, box plot-type graphs were chosen (Figure 1). The ANOVA one-way test was used for the comparison between stage III and stage IV in the area of self-care ($F_{1,59}=10.23$; $P<0.05$, partial $\eta^2=0.15$), mobility ($F_{1,59}=54.53$; $P<0.01$, partial $\eta^2=0.48$), and social function ($F_{1,59}=6.16$; $P<0.05$, partial $\eta^2=0.10$) of RTT. Significant differences were observed between the two groups of persons for all areas, indicating that persons with stage IV had the lowest scores.

Discussion

The functional abilities in RTT have gained much interest in the last decades.^{2,7,40,47} Results found in the literature

concerning the outcomes in RTT studies vary greatly; some studies report high percentages for some abilities, while other studies find different results. Although some discrepancies in these studies may be found, they all show the general capacity of individuals with RTT. However, until now, comparable functional abilities in persons with stages III and IV of RTT have not been systematically investigated using instruments such as the PEDI. In the present study we therefore examined through questionnaires and direct observation the functional abilities of 60 people with stages III and IV RTT who presented functional abilities related to the areas of self-care, mobility, and social function.

A common area of self-care that greatly influences the inability of RTT persons is the difficulty to functionally move the hands.^{2,7} Appearance of stereotypies interferes with voluntary hand functions, such as rubbing, wringing, or clapping of both hands at the midline in front of the chest or around the mouth.^{59–61} In the current study, 26.7% of persons evaluated were able to eat with their fingers, 5.0% were able to use a spoon, 25.0% were able to hold a feeding bottle or cup with a spout, 15.0% were able to raise a glass to drink, and 3.4% were able to firmly raise a glass without a lid using both hands. Mount et al⁶² observed in a series of 143 persons that 70.6% did not use hands with functional purpose. However, Fabio et al⁶³ found that the containment of manual stereotypies, postural control, and organization of external stimuli may be options for the functionality of RTT. Thus, while the area of self-care is fundamental to guarantee the basic conditions of daily living, the results show that RTT persons are unable to perform these basic living tasks, and therefore require a large amount of assistance from the family for most activities.

Table 3 Social function activities performed by at least one person with Rett syndrome

Able stage		Unable stage		Not applied n*	N**	Acquisition >90%, age range in years***	Activity****
III	IV	III	IV				
n (%)	n (%)	n (%)	n (%)				
38 (100)	22 (100)	0 (0)	0 (0)	–	1	0.6–0.11	Orients to sound
21 (55)	6 (27)	17 (45)	16 (73)	–	26	1.0–1.5	Shows awareness and interest in others
18 (47)	6 (27)	20 (53)	16 (73)	–	2	1.6–1.11	Recognizes own name or name of familiar person
15 (45)	0 (0)	18 (55)	22 (100)	5	56	2.0–2.5	Shows appropriate caution near stairs
10 (30)	1 (5)	23 (70)	21 (95)	5	61	2.0–2.5	Child may play safely at home without being watched constantly
10 (26)	3 (14)	28 (74)	19 (86)	–	16	1.0–1.5	Uses gestures with clear meaning
9 (27)	5 (23)	24 (73)	17 (77)	5	22	3.0–3.5	If upset due to a problem, the child needs to be helped
9 (24)	2 (9)	29 (76)	20 (91)	–	31	0.6–0.11	Notices presence of other children and may vocalize or gesture
6 (16)	3 (14)	32 (84)	19 (86)	–	3	1.6–1.11	Understands ten words
6 (16)	0 (0)	32 (84)	22 (100)	–	36	1.0–1.5	Manipulates toys, objects, or body with intent
4 (12)	0 (0)	29 (88)	22 (100)	5	62	3.0–3.5	Goes outside the house safely
4 (11)	1 (5)	34 (89)	21 (95)	–	17	1.6–1.11	Uses single word with meaning
4 (11)	0 (0)	34 (89)	22 (100)	–	6	1.6–1.11	Understands short sentences about familiar objects and people
3 (9)	0 (0)	30 (91)	22 (100)	5	11	2.0–2.5	Names objects
3 (9)	0 (0)	30 (91)	22 (100)	5	12	2.0–2.5	Uses specific words or gestures to direct or request actions

Notes: *Number of children without adequate age to perform the activity; **activity number appearing on the Pediatric Evaluation of Disability Inventory evaluation form; ***age range in years at which more than 90% of the typically developing children acquired this activity; ****the items are sorted in order of decreasing capacity and identified by the number of persons in stage III and IV able to perform the activity.

Considering mobility, persons with RTT who remain ambulant (stage III) have a characteristic gait, performed with the legs in extension and broadening the base of support. The steps are short and the hands remain clasped along the midline, with no reciprocal oscillation of the upper limbs. Sometimes, individuals in stage III RTT prefer to walk on tiptoe.⁶⁴ The lack of direction and planning gives the gait an apraxic character.⁶⁵ According to Segawa,^{27,66} who investigated 38 persons with RTT using an evaluation of the motor milestones, 47% were unable to walk outdoors without assistance. Colvin et al⁶⁷ found that 68% of 147 persons had never walked. Larsson et al³⁹ presented data on 119 persons evaluated, of whom 73% (87/119) learned to walk, but 20% stopped in the period of motor deterioration, others simply stopped walking, and of these, only 2% were able to relearn to walk.

In the current study, the PEDI was used to reveal different levels of ability in various functional abilities in mobility in

RTT persons (Table 2). Considering walking and posture changes that are presented by a majority of the articles related to mobility in RTT, 29 (71%) of the persons in stage III were able to walk in internal or external environments and 30 (79%) were capable of purposely changing physical location with difficulty. The ability to walk is important for the RTT persons because they do not need to be constantly accompanied by a caregiver in in-house and controlled environments and are able to explore spaces and areas with little or no assistance. However, in outdoor environments people with RTT must be supported by a caregiver. Larsson et al³⁹ found that even girls and women who were able to walk were unable to perform or had difficulty performing ordinary transitional movements.

Lotan et al⁴⁵ investigated the feasibility of a physical exercise program with a treadmill for four persons with RTT (stage III) in order to promote fitness and health and showed statistically significant improvement in areas of functional

Table 4 Comparison between the different areas (indicated with *P*-values) of the Pediatric Evaluation of Disability Inventory for each stage of Rett syndrome

	Self-care – mobility	Mobility – social function	Social function – self-care
Stage III	<0.001	<0.001	<0.001
Stage IV	0.041	0.281	<0.001

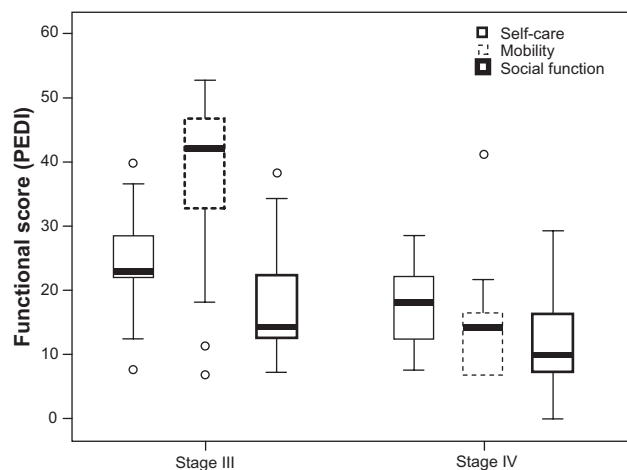


Figure 1 Comparison of the three areas (self-care, mobility, and social function) between persons with stage III and stage IV Rett syndrome.

Notes: Thick lines represent the medians of scores; the lines below and above represent the first and third quartiles, respectively.

Abbreviation: PEDi, Pediatric Evaluation of Disability Inventory.

ability such as knee walking, going up and down stairs, and walking at a speed over 25 m. Lifelong care for persons with RTT should include standing, weight bearing, and activity, since the majority of people with RTT today survive into adulthood.⁴⁷

In conclusion, our results demonstrate that the transfer from a lying to a sitting position, and then maintenance of a sitting position, are the functional abilities that the persons in stage III and IV were most able to perform. An incentive to change simple posture provides functional benefits for RTT persons. Thus, achieving the sitting position adequately is fundamental for improving the quality of life of these persons, as it is a functional position that the person maintains throughout the day.

With respect to social function in RTT persons, the absence of speech with simple maintenance of vocalizations and babbling was observed. As verbal skills are quite limited,² attention is necessary to recognize nonverbal forms of communication. Forms of nonverbal communication are usually very subtle in RTT persons.⁶⁸

Marschik et al,^{43,44} in contrast to the commonly accepted concept that these children are normal in the preregression period, found markedly atypical development of speech-language capacities, suggesting a paradigm shift in the pathogenesis of RTT and a possible approach to its early detection.

In this study, we observed that four persons (11%) in stage III and only one person (5%) in stage IV used a single word with appropriate meaning and that ten persons (26%) in stage III and three (14%) in stage IV used meaningful gestures. Segawa⁶⁶ reported that 53% of 38 persons studied

did not speak a word, and Halbach et al⁴⁸ in a longitudinal study about aging in RTT reported that 22% of 37 persons with RTT were at least sometimes able to express themselves by spoken language and/or signals. However, Larsson et al³⁹ reported 65% (75/115) of persons were able to, in some form, express what they wanted and Gratchev et al⁶⁹ reported that 34% of their 38 persons were able to pronounce a word. Although there are some differences in the reported findings with respect to speech in RTT persons, the difficulty of communication can be seen as a principal incapacity in RTT that hinders any social function. The inability to resolve problems along with difficulties in social interaction, self-protection, and community function are so great that total aid must be given by the caregiver for any basic needs.

The data in the current work indicate that the main difference between stage III and IV of RTT is in the area of mobility. Individuals in stage III have greater mobility than individuals in stage IV. These results appear to be expected, as the clinical stages of the disease indicate an increase in severity from stage I to stage IV. However, this is the first study that evaluates a significant number of persons with RTT using an evaluation system such as the PEDI, and through this assessment it is possible to discover important details in the areas of self-care, mobility, and social function. The knowledge of the capabilities of persons with RTT is important for organizing intervention programs and clarifying the functional abilities to families and the society.

The current study has several limitations worth noting. First, despite that the data fully represents the functional capabilities of the evaluated group, there are no studies on the validity and reliability of the PEDI in RTT, because this is the first study that uses the PEDI in this patient population. The second concern is in relation to the diagnostics and classification of RTT. Those data were obtained by a team of doctors, but unfortunately this study does not provide a *MECP2*-mutation diagnostic and classification division in stage IV (IVA and IVB). Moreover, RTT clinical assessment can generally contain errors in diagnostics and classification, which may have influenced some results. However, since all doctors involved are highly experienced we believe that this did not influence the results to a great extent. The third concern is the lack of data on different forms of therapy performed by patients, which can influence their performance in functional ability. We believe that future studies comparing therapies and functional abilities are relevant to the area. The fourth concern is the presence of outliers due to functional differences between people with RTT. The decision was made to keep the outliers in the results, even with the possibility of altering the mean and increasing variability.

Nevertheless, within the limits of these methodological caveats, the results presented here do allow for new insights into the functionality of persons with RTT. This study characterizes the functional abilities of stage III and IV RTT persons and shows differences between the two stages by using a standard international assessment that is used in different diseases. The use of the PEDI enables a verification of the real abilities of persons through the questionnaire and direct observation of persons, giving important data to professionals who work directly with RTT rehabilitation programs. The use of the PEDI also enables professionals to inform families about the difficulties and functional perspectives, providing a greater comprehension of the disease.

Conclusion

We suggest that the clinical features of RTT are indicative of a disabling disease, which leads to particular challenges for professionals working in rehabilitation. This conclusion is based on the finding that RTT severely impairs motor function due to the presence of scoliosis, osteotendinous retractions, and progressive immobility at the later stages of the disease (stage IV). In addition to motor impairment, cognitive changes are also evident in this population, and changes associated with musculoskeletal disorders may negatively impact the level of functional independence of individuals with RTT. Although persons with stage III RTT have better functional abilities when compared with stage IV, the areas of mobility, self-care, and social function are quite affected, which shows a great functional dependency and need for help in basic activities of daily life.

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Disclosure

The authors report no conflicts of interest in this work.

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