An intensive Anti-Scoliosis Postural Intervention Supported by an Application for Individuals with Rett syndrome

Document date: 22/07/2022

Abstract

Background: Scoliosis is the most common orthopedic comorbidity in Rett syndrome (RTT), with a prevalence of 94% and a mean curve progression of 14-21° Cobb annually. A scoliosis prevention intervention based on daily activity programs was proposed for people with RTT within uncontrolled study designs.

Aim: The current study aims to evaluate the effectiveness of a home-based activity program carried out during daily life to slow the progression of scoliosis in girls with RTT.

Ethics: The proposal was approved by Ariel university IRB. All participants' parents will sign informed consent forms.

Participants: Twenty Italian girls aged between six and 16 years with a genetically confirmed classic RTT and scoliosis at a severity level between 10° and 40° Cobb will be recruited and randomly divided into two groups (immediate intervention – Group 1; wait-list-intervention – Group 2). Both groups will follow the same 10-month intervention program, 10 months apart.

Outcome measures: Participants' scoliosis Cobb's angle, motor functioning, and behavioral characteristics will be assessed three times.

Procedure: The interventions will comprise daily home-based activity programs carried out by participants' caregivers within everyday living environments. An expert therapist will remotely supervise each program through an ad hoc developed smartphone application.

Table of contents

Introduction

Rett syndrome (RTT) is a severe neurodevelopmental disease caused by a mutation in the MECP2 gene located on the X chromosome,[1] affecting about 1/10,000 females worldwide.[2–4] Scoliosis is the most common orthopedic comorbidity in RTT,[5–7] showing a prevalence of up to 94%.[7–11] Reported median age of scoliosis onset in RTT is at 9.8 years, with 25% of subjects affected by the age of 6 years, about 79% by the age of 13 years, and 85% by the age of 16 years or older.[7,9,12,13] Scoliosis in RTT is neurogenic in origin and can result in pain, loss of sitting balance, deterioration of motor skills, and progressive restrictive lung disease development.[14] Diminished early development, inability to sit and walk without support, the onset of puberty, and enhanced clinical severity are also associated with developing scoliosis at an early age.[11,13,15]

The case literature suggests a fast mean curve progression in this population ranging from 14° to 21° Cobb per year, accompanied by an acceleration in the progression at puberty with an average age of 13 years.[11,14,16] Moreover, in a large cohort study analyzing radiographs of 128 girls and women with RTT followed for two years (three radiographs for each subject), the magnitude of scoliosis was found to generally increase with age with a yearly 0.438-unit increase in the square root of the baseline Cobb's angle (95% Confidence Interval 0.374 – 0.503).[17]

A corset is usually suggested for individuals with RTT with Cobb's angle greater than 20-25°, and spinal fusion is considered if Cobb's angle progresses over 40-50°.[12,15,18]

Spinal surgery is considered the definitive management of neuromuscular scoliosis.[19] In most cases, posterior-only spinal fusion is performed.[20] However, if an anteroposterior surgery is required, a single-stage approach is preferable to reduce anesthetic and surgical complications.[12] Fixation to the pelvis is indicated in non-ambulant children with pelvic obliquity[12] and in the presence of a preceding rapid decline in neurological function with a lethargic presentation and uncontrolled, treatment-resistant daily seizures.[21] Surgery should not be delayed until skeletal maturity has been achieved. Barney and colleagues suggested the need for RTT-specific postoperative pain management.[22] The authors reported that, after spinal fusion, patients with RTT received fewer total doses of opioids compared to girls with cerebral palsy and idiopathic scoliosis. With modern technology, severe curves can be safely treated,[21] and positive outcomes following spinal surgery were reported.[23–26] Even so, the decision to perform the operation is challenging for the family due to anxiety about their daughter undergoing such a complex medical procedure.[8,24] Moreover, a large cohort study reported that 18.5% of subjects with RTT

and scoliosis had spinal instrumentation,[15] showing that the vast majority of this group of clients will not undergo surgery and therefore will rely on non-surgical, conservative treatment. Thus, the development and evaluation of such programs are critical for individuals with RTT.

Background

Available conservative interventions for scoliosis include observation and monitoring, bracing, orthotics, and physical therapy.[27–29] As specific guidelines for the management of scoliosis for people with RTT were published,[12] the available treatments for scoliosis were here described in the light of such guidelines. The scoliosis monitoring for these patients should start before the diagnosis of scoliosis. Before-diagnosis monitoring strategies for people with RTT include genetic testing, parental teaching on the characteristic aspects of scoliosis, and physical assessment upon the diagnosis of RTT and at least every six months thereafter.[12] After diagnosing scoliosis, yearly spine radiographs are suggested to monitor the curve progression. The collection of radiographs every six months is recommended if Cobb's angle progresses over 25° before the skeletal maturity. The maintenance of physical examinations every six months is advised after the scoliosis diagnosis.[12] Bracing strategies were suggested in the literature for neuromuscular scoliosis management among its conservative treatments. A recent literature review identified 23 typologies of braces proposed to care for scoliosis curves of different types ("C" or "S" shaped), levels (thoracic, lumbar, and thoracolumbar), and entities, using different approaches (passive and active correction).[30] Indications for bracing are stronger in younger children and more controversial in adolescents. Bracing aims to contain the curve until skeletal maturity[31] and regain the sitting position.[32] However, the role of bracing in patients with neuromuscular scoliosis is contentious, and there is no compelling evidence supporting the use and success of braces in preventing the deformity progression in neuromuscular scoliosis.[19,32] There is no consensus among experts on RTT that bracing is beneficial in reducing the scoliosis progression in this population.[12] Nevertheless, bracing may be valuable if support is needed in a sitting position (usually for extremely hypotonic children who find it difficult to maintain an erect posture for long periods) or delay the necessity of surgery.[12,33,34]

When considering conventional interventions regarding scoliosis, there is a consensus among experts that efforts should be made to maintain the ability to walk and increase the duration and distance walked to counteract the curve progression.[19,27,35] However, the capacity of physical therapy treatments to reduce scoliosis or prevent mild scoliosis from

rapidly progressing has received scarce consideration in the literature.[35] Although so far, physical therapy interventions have not been found to improve etiological factors for neuromuscular scoliosis or prevent progression of established scoliosis, they were reported as helpful in avoiding any adverse effects, such as: prolonged brace use, prevention or prolonging onset of joint contractures, and maintenance of both chest mobility and respiratory excursion.[27,32] The implementation of physical therapy for scoliosis must be based on the particular spinal deformity characteristics and requires specifically trained therapists and clinicians.[28]

To our knowledge, only one anti-scoliotic physical therapy intervention explicitly directed to patients with RTT was proposed in the literature.[35] This is a specific physical therapy regimen comprised of an intensive program of postural positioning and enhanced activity level carried out in cooperation with the participant's family members and caregivers (within the educational facility). The intervention was conducted with a 5-year-old girl with RTT whose Cobb's angle reduced from 30° to 20° over an 18-month treatment period through the use of positioning equipment, postural strategies (activating automatic equilibrium reactions, which oppose the natural scoliotic curve), and a motor activity program (walking or standing) during waking hours. This result was maintained for three years until the routine mentioned above ceased, when the child's scoliosis rapidly regressed. A recently published article from Romano et al. [36] replicated this intervention method with 20 participants with RTT in Italy and reported no change in scoliosis severity for this group of clients during a one-year follow-up. Thereby strengthening the validity of the approach proposed by Lotan, Merrick, and Carmeli.[35] Moreover, previous programs were found helpful in increasing the motor function of five girls with RTT in Ireland,[37] 17 girls and women with RTT in Italy,[38] and 40 individuals with RTT in northern Italy.[39] This accumulation of evidence provides initial evidence of the feasibility and acceptability of this type of treatment in a broad age range and a wide functional range of participants.

The intervention proposed in the current protocol is ecological and intensive in nature, will be carried out by primary caregivers within the participants' daily living environment (home and educational facility), and will be planned and supervised by therapists experienced in treating individuals with RTT. Moreover, the authors will remotely supervise the intervention by using an ad hoc developed smartphone application.

Study Aim

The current study aims to evaluate the effectiveness of an anti-scoliotic physiotherapy program carried out during daily life and focuses on hypercorrective postures and on increasing the level of activity to assess whether or not it is possible to slow the progression of scoliosis in girls with Rett syndrome (RTT).

The current research project has the following research objectives:

- Primary objectives:
    1. Build, implement and evaluate a physiotherapy program for contrasting scoliosis trajectory adapted to individuals with RTT;
    2. Develop a secondary deformity prevention program through early intervention for people with RTT.
- Secondary objectives:
    1. Build and evaluate the efficiency of a support application for carrying out rehabilitation exercises;
    2. Explore the factors influencing adherence and implementation of intervention from the perspective of both families and therapists in light of the above-mentioned application.

Research Questions

- Can an individualized, remotely supervised physiotherapy program contrast the scoliosis progression of girls with RTT?
- Can a smartphone application support the adherence and the implementation of an individualized activity program carried out at home by caregivers of girls with RTT?
- Can the use of the application reduce the costs of remote supervision?
- Which factors influence the adherence and implementation of the intervention from the perspective of both families and therapists?

Materials and Methods

Study Design

A randomized controlled study with a waiting list design will be applied.

Study Population

For this study, 20 girls aged between six and 16 years with genetically confirmed classic RTT and scoliosis will be recruited from the San Paolo Hospital (Milan, Italy) or the Italian Rett Association (AIRett – Verona, Italy).

Sample Size and Power Calculation

The information available in the literature suggests that the Cobb angle in RTT typically increases by approximately 14 ± 8° Cobb per year. Based on these data, an alpha of 0.05 and a beta of 0.8, we estimate that for this study, the researchers will need a sample size including two groups of 10 subjects and that statistical significance will be achieved if both groups of participants will show an average increase in the scoliotic curve of less than 12° Cobb after the implementation of the proposed program.

Inclusion Criteria

- Diagnosis of RTT with confirmed MECP2 gene mutation;[40]
- Diagnosis of unstructured flexible scoliosis (Cobb angle between 10° and 40°) measured radiologically with an x-ray performed no more than six months before the recruitment;
- Age between 6 and 16 years.

Exclusion Criteria

- Presence of psychomotor developmental deficit evidenced in the first six months of life or diseases of neurometabolic, infectious, or secondary brain damage trauma origin;
- Previous surgical intervention to the spine or its planning within the study period;
- Use of a corset during most waking hours;
- Clinical judgment of the evaluating specialist doctor who certifies unstable health conditions that are not compatible with the performance of the rehabilitation program (e.g., ongoing or recurrent infections, severe gastrointestinal disorders, drug-resistant epilepsy with multi-day seizures).
- Clinical judgment of the research team suggesting an inability of the home environment to perform the intervention program (change in residence, a planned pregnancy, a pre-planned complex surgical/medical procedure within the period of the planned intervention program for the child of family memeber) within the intervention period.

Ethical Issues

The Ariel University Institutional Review Board (IRB) approved the study (no. AU-HEA-ML-20201019 – See IRB approval in Appendix 1) that will be conducted according to the ethical principles of the Helsinki Declaration and local regulations. All details relating to the study procedure will be discussed with participants' parents or legal representatives, and an informed consent form (See Appendix 2) will be signed for all. Enrolment will be voluntary, with participants not receiving any incentives, financial or otherwise, for participation.

Study Protocol

The participants' parents will receive an information sheet regarding the study and informed consent for participation and collection of video materials at the recruitment. A reference telephone number and an e-mail address will be provided to be contacted in case they would like further information or would like to communicate the exit from the study. The eligibility of the candidates will be assessed at the time of recruitment (T1) through an initial neurological or physiatrist evaluation. At the same time, each participant will undergo a rehabilitation evaluation to collect the outcome measures (see section "Data collection") and create an individualized intervention plan specific to the participant's scoliosis, functional abilities, and parental/educational setting's availability. During the evaluation, the postural needs of the participants will also be identified, and a qualified technician will build or adjust the positioning devices, making them suitable for each intervention plan. Using block randomization, participating girls will be randomly divided into treatment (Group 1) or delayed treatment (Group 2) groups. Participants in Group 1 will begin carrying out the rehabilitation program immediately after the first assessment session (T1). Each program will require the daily performance of different postures and therapeutic activities at the girls' educational facilities and homes, based on the availability of families, for a duration of 10 months. Specific strategies that will be implemented will include maintaining asymmetrical postures that oppose the scoliosis curve during activities and exercises in sitting, standing, and walking positions (according to each participant's functional abilities). These strategies refer to a hypercorrective postural positioning of scoliosis. In addition, activities involving weight bearing on the lower limbs, such as walking and standing for at least two hours a day, will be encouraged, and passive stretching and spinal mobilization exercises will be conducted.

Participants' parents and local reference physiotherapists who will supervise the program in the educational or home setting will be involved in training sessions aimed at learning the performance of the child's program activities. In addition, a smartphone "ActivRett" activity application will be constructed for this research. The application will be downloaded and used by the group that takes care of each participant. It will contain the participant's individualized therapeutic indications and allow the collection of data relating to the development and execution of the program. Further support for parents, caregivers, and therapists will be provided via Skype by an Italian therapist (AR) experienced in treating individuals with RTT at the program's start and after every two months. These meetings will be aimed at discussing the progress of the program, solving problems, reorganizing schedules, adjusting the suggested exercises, assessing the achievement of objectives, and, if needed, setting additional goals.

At the end of the intervention of Group 1 (10 months after its start), the outcome measures will be collected again for all participants (T2), and those in group 1 will be allowed to continue using the application yet without receiving the above-mentioned skype calls. Then, those included in Group 2 will be reevaluated and start to actively participate in the planned intervention, which will be carried out for the second period of 10 months. At the end of the intervention phase of Group 2, the outcome measures will be collected again for all participants (T3), and the data obtained will be analyzed by the researchers. At the end of each intervention phase, a specific questionnaire will be administered to the parents, therapists, teachers, and other caregivers involved in the intervention program mentioned above to assess the participants' satisfaction with different aspects of the intervention conducted. The research timetable is outlined in Appendix 3.

Outcome measures

Anamnestic Information

The anamnestic information collected for each participant will include age, age at diagnosis of scoliosis, the amount of motor therapy interventions received, and the type of genetic mutation (see data collection sheet in Appendix 4).

Rett syndrome severity level

The Rett Assessment Rating Scale (see RARS form in Appendix 5) will be used to evaluate the severity of RTT clinical manifestation at T1. The RARS is a 31-items RTT-specific severity scale.[41] Each item concerns a specific phenotypic RTT characteristic. The

total score indicates the participant's RTT severity level ranging from a mild deficit (reflected by lower scores) to severe symptoms (reflected by higher scores). A standardization procedure for the Italian population with RTT was conducted for the RARS. Skewness and kurtosis values, calculated for the total score distribution, were 0.110 and 0.352, respectively. The distribution was found to be normal. Internal consistency for the total score (0.912), as well as for the subscales, was high (0.811–0.934).[41,42]

Scoliosis Progression

The progression of scoliosis will be assessed during the study by measuring Cobb's angle on three anteroposterior X-rays of the spine collected respectively at T1, T2, and T3. The girl will be positioned in the most upright position comfortable for her. The angle will be measured using standard procedures. If the participant has an X-ray examination of the spine carried out in the manner prescribed for this study in the six months prior to the start of the intervention, this radiograph will be used as a pre-intervention examination. If the participant does not have an x-ray examination with the characteristics described above, it will be carried out as part of this project in compliance with the international guidelines for the management of scoliosis in RTT, which provide for the carrying out of six-monthly radiographic examinations in the presence of evolving scoliosis.[12] Moreover, the radiographic examinations carried out periodically by the participants before the recruitment at the participants' reference hospitals will be collected by the researchers to allow the extraction of data relating to the evolutionary trajectory of scoliosis up to the time of recruitment. The Cobb's angle will be obtained from the average value of three measurements carried out by independent blinded (to the treatment status of each subject) medical specialists with clinical experience concerning scoliosis in RTT. Using the results provided by different clinicians blinded to the procedure, the date of the x-ray is taken, and the functional state of each participant will allow a more reliable final measurement.[43]

Adherence to the Program

The compliance with the intervention will be measured through the smartphone application. This will allow an assessment of the amount of treatment received, which is essential for calculating the correlation between the number of therapeutic activities performed and the variation of Cobb's angle.

Gross Motor Function Level

The gross motor function level, including the ability to walk, will be measured during the rehabilitation assessments using the Rett Syndrome Motor Evaluation Scale (RESMES – Appendix 6). This scale includes 25 items that examine motor function divided into six sections: standing, sitting, postural transfers, walking, running, and climbing / descending stairs. Sixteen items are rated on a discrete scale, ranging from 0 (indicates no or very mild impairment) and 4 (severe impairment). Nine items related to walking skills are evaluated on a discrete scale with a score from 0 to 2 where 0 indicates that the activity could always be completed by the subject and 2 that is assigned if the item cannot be carried out. The items' scores are added together, thus giving a total RESMES score (range: 0 to 82). Moreover, a score for each section can be calculated. Additionally, the RESMES was designed to be completed by the primary caregivers of the person with RTT. Comparing the total score obtained by parents and doctors revealed a high correlation and no statistically significant difference.[44] This scale was recently validated on a sample of 60 girls and women with RTT (mean age: 12 years 5 months SD: 8 years 9 months; range: 3–40 years), showing optimal agreement between the assessors and strong internal consistency (reliability coefficient = 0.96 SD = 0.18; Cronbach's alpha coefficient for the full scale = 0.95 CI 0.93–0.97).[45]

Behavioral Characteristics

The behavioral characteristics of the participants will be evaluated at T1, T2, and T3 through the administration of the Rett Syndrome Behavior Questionnaire (RSBQ - Appendix 7).[46] The RSBQ is a questionnaire created by comparing the behavioral characteristics of people with RTT with those of individuals with severe intellectual disability. The questionnaire is filled in by parents who are asked to provide an evaluation of the behavioral characteristics shown by their child at the time of completion. Because people with RTT suffer from severe physical and cognitive deficits linked to behavioral and emotional disturbances, the RSBQ includes elements describing behavioral characteristics and assessing physical capabilities, including hand function and sitting and walking skills. Other items evaluated by the questionnaire include sleep disturbances, respiratory difficulties, mood disturbances, self-harm, social skills, and stereotyped hand movements. The Chronbach's alpha for the RSBQ was high (>0.90) for the RSBQ total score and moderate (0.60–0.79) to high for all the sub-scales. The questionnaire test-retest reliability was assessed by calculating intra-class correlations between two completions of the questionnaire. Intra-class correlations

were high (>0.80) or moderate (0.60–0.79) for the RSBQ total score and all the sub-scales.[46]

Caregivers' Burden

The burden related to the implementation of the treatment will be assessed through the administration, at the end of the study, of a questionnaire to all parents, therapists, teachers, and other caregivers involved in the intervention. The items included in this questionnaire will address the burden derived from the treatment implementation, the parental satisfaction, and the intervention's perceived efficacy concerning functional skills and posture of the trunk and spine. The same questionnaire was successfully used when evaluating previous results of a few remote rehabilitation research with individuals with RTT.[38,47]

Statistical analysis

The normality of each variable's distribution will be assessed using the Shapiro-Wilk normality test. The ages, amount of received physical rehabilitation interventions, scoliotic curve degrees, behavioral characteristics, and activity and gross motor functional levels obtained at T1 will be compared between the two groups to assess their comparability through Wilcoxon's signed-rank test or Student's T-test (dependent of the variable distribution characteristics). Changes that occurred in the variables of each group at T1, T2, and T3 will be evaluated with Friedman's test or with the repeated measure ANOVA (dependent on the variable distribution characteristics). Between groups comparison for each variable collected at T1, T2, and T3 and for their variations that occurred between T1 and T2 and between T2 and T3 will be conducted using the Wilcoxon's signed-rank test or Student's T-test (dependent of the variable distribution characteristics), applying an appropriate adjustment for the age and gross motor skills of the participants. Relations will be searched between variables collected at T1 and the changes in the scoliosis curve degree and motor functioning after the treatment using Spearman's rank correlation coefficient or Pearson's correlation coefficient (dependent on the variable distribution characteristics). Moreover, a relation between the compliance with the proposed program and the changes in the scoliosis curve degree and motor functioning after the treatment will be searched using the Spearman's rank correlation coefficient or Pearson's correlation coefficient (dependent on the variable distribution characteristics). The threshold for significance of the above-described analyses will be set at $\alpha = 0.05$. No correction for multiple comparisons will be applied.[48]

Importance of the Research

The current study is of high importance for the population with RTT as no established conservative treatment is available for scoliosis prevention in RTT. Previous findings suggested that intense daily-based activity programs hold the potential to reduce the scoliosis progression in people with RTT and, in some cases, to reduce the scoliotic curve.[35,36] However, the proposed study will be the first attempt to prove the efficacy of such programs within a randomized controlled trial where the control group is enrolled as a waiting-list group. The results gathered from the current protocol will add to the existing literature supporting the implementation of a supervised activity program for all individuals with RTT urging clinicians to provide this service to their clients with RTT. Moreover, the information obtained from the current research will allow the researcher to identify the fundamental elements that can incentivize or limit the effectiveness of these activity programs, allowing the creation of guidelines for the construction of such individualized programs.

Moreover, the application developed within the current project will represent a valid and reliable tool to support and monitor the development of the activity programs in a home-based environment, thereby enabling all the involved professionals to closely follow their clients and caregivers to have all the information necessary for the program's implementation available. The developed application will be available in five languages (Italian, English, Hebrew, Arabic, and Russian), allowing its use across several countries. Moreover, we trust that such an application can be a significant incentive to families and support teams for many with disabilities, thereby enabling adherence to remote rehabilitation programs with minimal costs.

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Appendix 1 – Ariel University Institutional Review Board approval

ARIEL UNIVERSITY

Approval of the Ethics Committee for Non-Medical Studies

To: Prof. Meir Lotan

Physical therapy department,

Ariel University, Israel

We are convinced that the study, as detailed below, is not a medical experiment involving human participants, and that it upholds the conditions detailed in the procedure for approval of studies that are not medical experiments involving human participants.

A) Details of the study:

Name of main researcher: Prof. Meir Lotan
Title of the research: An intensive anti scoliosis postural intervention, measured by an application, for individuals with Rett syndrome.

B) This certificate of approval is valid from October,19,2020, until October 18, 2021.

C) Conditions and limitations: Participants must sign a letter of consent.

Committee members of the School of Health and Medical Sciences:

Chairman of The University Ethic committee:

Prof. Yair Shapiro

Date: 10/19/2020

No. of Approval: AU-HEA-ML-20201019

Appendix 2 - Informed consent form

Title of the study:

An intensive Anti-Scoliosis Postural Intervention Supported by an Application for Individuals with Rett syndrome

I, the undersigned _____

Legally recognized family member / representative.

as _____

Indicate the relationship with the patient (legally recognized family member / representative).

of _____

Surname and Name of the patient.

born in, on: _____

Place and date of birth of the patient.

DECLARE THE FOLLOWING:

1. I have read and understood the Patient Information Sheet;
2. I received complete explanations on the clinical study from Dr. _____ (investigator or authorized member of the team) to whom I had the possibility to ask questions and explanations and from whom I received satisfactory answers to my questions;
3. I was told the nature, purpose, and duration of the study, the procedures that will be adopted for carrying out the research, and the type of collaboration that will be required;
4. I understand that the participation of the patient I represent is free and voluntary and that at any time, I can decide to terminate her participation and withdraw her from the research without having to provide justification, without her being deprived in any way of care and assistance she needs or access to new diagnostic and / or therapeutic perspectives,

and without compromising her rights and her relationship with the involved doctors, health professionals, and technicians;

5. I understand that the staff of the department (doctors and physiotherapists) and those engaged in the research will be able to view - under the direction and with the authorization of the doctor in charge of the study - the data collected relating to the patient;

6. I accept that, as part of this research project, video recordings of myself and my daughter can be made and that these can be used anonymously for research purposes, in congresses and conferences, and for professional development;

7. Under the Italian Legislative Decree 196/2003 and subsequent amendments, I agree to the collection, analysis, opening and transfer of my data (including the transfer outside the European Economic Area) for health care or medical research purposes.

Understood all this, in my full capacity to understand and want, and without any form of conditioning or coercion, I confirm that I agree to the patient's participation, of which I am the legally recognized Representative in the study described in this document.

Signature of the legally recognized family member / Representative:

_____

Place and date: _____

PART RESERVED TO THE INVESTIGATOR OR AUTHORIZED MEMBER OF THE TEAM:

I, the undersigned Dr. _____

(Surname and Name).

declare:

a. to have explained to the legally recognized Representative the nature and purpose of the research as well as the procedures that will be adopted and the type of collaboration that will be requested;

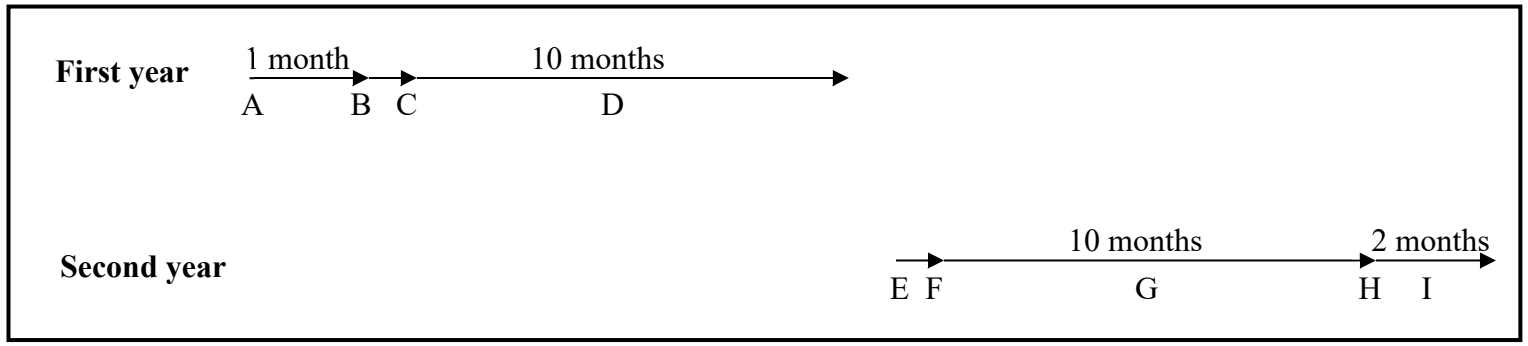
b. not to have tried to influence or force in any way the legally recognized Representative to induce him / her to give his / her consent to the patient's participation in the research;

c. to have issued to the legally recognized Representative a signed and dated copy of this form and the information sheet.

Place and date: _____

Signature: _____

Appendix 3 – Research timetable



A. Organize the research: gather the participants, obtain the IRB approval in Italy, and prepare the forms.

B. Evaluation of each participant. Construction of the individualized equipment for postural alignment and a workshop for parents / caregivers / therapists from Group 1 (one week).

C. Start of the intervention for Group 1.

D. Intervention in progress for Group 1 with supervision via Skype calls and Group 2 waiting-list phase.

E. Evaluation of each participant.

F. Construction of the individualized equipment for postural alignment and a workshop for parents / caregivers / therapists from Group 2 (one week).

G. Start of the intervention for Group 2.

H. Intervention in progress for Group 2 with supervision via Skype calls and Group 1 follow-up.

I. Evaluation of each participant.

J. Summary of results.

Appendix 4 – Anamnestic information data collection sheet

An intensive Anti-Scoliosis Postural Intervention Supported by an Application for Individuals with Rett syndrome

Dear family,
we kindly ask you to fill in this anamnestic questionnaire for participation in the research you have joined and send it to Airett (email: centrorett@airett.it).
AIRett will send the questionnaire to Dr. Marina Rodocanachi, the doctor responsible for the clinical aspects of the research, from which you will then be contacted to arrange a remote interview for verification of the clinical aspects relating to participation. A possible physiatric examination of your daughter can subsequently be scheduled at the San Paolo Hospital in Milan.

Compilation date: ___/___/_____
Name and surname of your daughter _____
Residence address: _____
_____
Name, surname and telephone number of parents: _____
_____
Parents' email address: _____
Name, surname and contact (telephone or email) of the therapist:_____
_____
Name, surname and contact (telephone or email) of the referring general practitioner: _____
_____

DEMOGRAPHIC DATA
Date of birth (dd/mm/yyyy)
Current head circumference:
Current weight:
Current height:

ANAMNESTIC DATA		
Duration of pregnancy	Full-term☐	Preterm ☐
Head circumference at birth (cm):		
Deceleration of the head circumference in the first year of life	**YES ☐**	**NO ☐**

Psychomotor development in the first year of life:		
– delay from the first months of life	**YES ☐**	**NO ☐**
– regression in the first six months of life	**YES ☐**	**NO ☐**
– regression within the first year of life	**YES ☐**	**NO ☐**
– late regression (after the first year of life)	**YES ☐**	**NO ☐**
– First regressive symptom highlighted by the family:	When:	
– First symptom of motor regression:	When:	

Genetic mutation

MECP2 gene mutation code:

……..……...……

Exam performed at:

…….…….…….....……..……..

Education (current year of school attendance):		
Attendance at a day center for people with disability	**YES ☐**	**NO ☐**
If yes, for how many hours?		
Rehabilitation activity	**YES ☐**	**NO ☐**
If there is currently no ongoing rehabilitation project, has there been in the past?	**YES ☐**	**NO ☐**
If yes, indicate the year of start and end of treatment:		

If at least one rehabilitation intervention is in progress, circle the number of times a week your daughter receives therapy sessions from a rehabilitation professional (therapist)							
Intervention	**Weekly sessions**				**Duration of each session**		
Physiotherapy	1	2	3	4	<30 min	30-45 min	>45 min
Hydrotherapy	1	2	3	4	<30 min	30-45 min	>45 min
Occupational therapy	1	2	3	4	<30 min	30-45 min	>45 min
Psychomotricity	1	2	3	4	<30 min	30-45 min	>45 min
Speech therapy	1	2	3	4	<30 min	30-45 min	>45 min
Music therapy	1	2	3	4	<30 min	30-45 min	>45 min
Hippotherapy	1	2	3	4	<30 min	30-45 min	>45 min
Osteopathy	1	2	3	4	<30 min	30-45 min	>45 min
If your daughter receives other rehabilitation interventions not mentioned, please specify them below							
Intervention:	1	2	3	4	<30 min	30-45 min	>45 min
Intervention:	1	2	3	4	<30 min	30-45 min	>45 min

The patient uses augmentative communication:	**YES ☐**	**NO ☐**
Frequency of augmentative communication (indicate the number of times per week or month):		
Duration of the augmentative communication (in years):		

The patient does music therapy:	**YES ☐**	**NO ☐**
Frequency of music therapy (indicate the number of sessions per month):		
Duration of music therapy (in years):		

CLINICAL SITUATION

1. Epilepsy

0. Not present	1. Single or sporadic seizures (no drug treatment)	2. Controlled by drugs	3. Not controlled (drug-resistant)

– Current frequency of seizures (if any):

0. Sporadic	1. Multi-monthly	2. Multi-weekly	3. Multi-daily

– Current antiepileptic therapy: ……
……
……

2. Sleep disorders

0. Not present	1. Mild	2. Moderate	3. Severe

What type of sleep disorder is present? (indicate even more than one):		
Awakenings at night	**YES ☐**	**NO ☐**
Difficulty falling asleep	**YES ☐**	**NO ☐**
Insomnia throughout the night	**YES ☐**	**NO ☐**
Early awakening in the morning	**YES ☐**	**NO ☐**
Daytime sleepiness	**YES ☐**	**NO ☐**
Others		

– Current therapy for sleep disorder: ……
……
……

3. Behavioral problems

0. Not present	1. Mild	2. Moderate	3. Severe

What type of behavior disorder? (indicate even more than one):		
Night agitation	**YES ☐**	**NO ☐**
Daytime agitation	**YES ☐**	**NO ☐**
Changes in mood (depressive symptoms)	**YES ☐**	**NO ☐**
Others		

– Current therapy for behavioral problems: ……
……
……

4. Respiratory problems

0. Not present	1. Mild	2. Moderate	3. Severe

What type of breathing disorder is present? (indicate even more than one):		
Apneas	**YES ☐**	**NO ☐**
Hyperventilation	**YES ☐**	**NO ☐**
Others		

– Current therapy for respiratory problems: ……
……
……

5. Gastrointestinal problems

0. Not present	1. Mild	2. Moderate	3. Severe

What type of gastrointestinal disorder is present? (indicate even more than one):		
Constipation	**YES ☐**	**NO ☐**
Gastroesophageal reflux	**YES ☐**	**NO ☐**
Abdominal distension due to aerophagia	**YES ☐**	**NO ☐**
Lack of appetite	**YES ☐**	**NO ☐**
Bruxism	**YES ☐**	**NO ☐**
Other: (e.g., Tube feeding, PEG, gastrostomy...)		

– Current therapy for gastrointestinal problems: ……
……
……

6. Nutrition

WHAT she eats / Preferences / Refusal: ……
……
……
……

She is fed with (check one or more boxes): □ Liquid □ Semi-solid □ Solid

Does she chew?	**YES ☐**	**NO ☐**
Does she lose food from the mouth?	**YES ☐**	**NO ☐**
Does she bring food to her mouth?	**YES ☐**	**NO ☐**
Others		

How she drinks: ……..……
……
……

Describe the duration of the meal (e.g., very short, prolonged...): ……
……
……

Do parents think she is well fed: ……
……
……

7. Musculoskeletal problems

0. Not present	1. Mild	2. Moderate	3. Severe

What type of musculoskeletal problem is present:		
Scoliosis	**YES ☐**	**NO ☐**
Joint deformities	**YES ☐**	**NO ☐**
Has she ever had a spine x-ray?	**YES ☐**	**NO ☐**
Date of the last radiograph: *		
Has she ever had a pelvis x-ray?	**YES ☐**	**NO ☐**
Date of the last radiograph: *		
Have you ever had a lower limb x-ray?	**YES ☐**	**NO ☐**
Date of the last radiograph: *		
Joint deformities	**YES ☐**	**NO ☐**
Surgery for scoliosis	**YES ☐**	**NO ☐**
Joint deformity surgery	**YES ☐**	**NO ☐**
Botulinum toxin	**YES ☐**	**NO ☐**
Wear a brace for the scoliosis	**YES ☐**	**NO ☐**

* it is helpful to bring the most recent radiographs to the clinical evaluation

8. Walking:

0. Normal	1. Compromised	2. Acquisition lost	3. Never acquired

If she walks, she does it:	**Independently ☐**	**With support ☐**
First steps (age):		
Age at which she stopped walking:		
Use the wheelchair:	**YES ☐**	**NO ☐**
Use other aids (describe below):	**YES ☐**	**NO ☐**

If yes, describe which aids she uses: ……

……

……

9. Assistive devices

Orthotics / Shoes	**YES ☐**	**NO ☐**
AFO	**YES ☐**	**NO ☐**
Upper limb brace	**YES ☐**	**NO ☐**
Corset (specify the type and the hours of use)	**YES ☐**	**NO ☐**
Custom-made chair	**YES ☐**	**NO ☐**
Positioning system	**YES ☐**	**NO ☐**
Stroller	**YES ☐**	**NO ☐**
Outdoor wheelchair	**YES ☐**	**NO ☐**
Standing frame	**YES ☐**	**NO ☐**
Walker	**YES ☐**	**NO ☐**
Lifter	**YES ☐**	**NO ☐**
Shower wheelchair	**YES ☐**	**NO ☐**
Bed	**YES ☐**	**NO ☐**
Other devices (theratogs, functional bandages…)		

10. Verbal communication:

First words (age): ……..……

Currently: ……

……..……..……

……

Does she use phrases?	**YES ☐**	**NO ☐**
Does she use single words?	**YES ☐**	**NO ☐**
She does not speak	**YES ☐**	**NO ☐**

Age at which she stopped talking: ……..……

11. Other aspects of clinical-health interest and related therapies:

……

……

……

……

……

……

……

12. Other accesses to medical services not yet mentioned (e.g., hospital or first aid admissions, surgeries that took place in the previous year). Indicate the type of intervention and the reason for access:

……

……

……

……

……

……

……

13. Other medications in use not listed above:

……

……

……

……

……

……

……

Signature of the authorized member of the team

_____

Parent's signature

_____

We thank you for your attention and time dedicated

Appendix 5 – Rett Assessment Rating Scale (RARS)

R.A.R.S. is a tool developed to assess the level of seriousness of the illness in girls suffering from Rett syndrome. It comprises 31 points concerning the various behavioural areas, each of which will be assigned a variable score from 1 to 4. The sum total of the scores will give an overall value determining a slight, average or high seriousness of Rett syndrome.

COGNITIVE AREA

I. Attention:

1	1.5	2	2.5	3	3.5	4
The girl has a constant attention span over time, in other words there is not alternation between a state of excitability and a state of calm.		The girl has slight difficulty in maintaining attention over time, in other words there is no significant alternation between a state of excitability and a state of calm.		The girl often has difficulty in maintaining attention over time, in other words there is frequent alternation between s state of excitability and a state of calm.		The girl has excessive difficulty in maintaining attention over time, in other words there is a significant alternation between a state of excitability and a state of calm, leading to selective attention deficiency.

II. Spatial orientation:

1	1.5	2	2.5	3	3.5	4
If the girl is asked to look at or go to the kitchen or another location without assistance, she orients herself well.		If the girl is asked to look at or go to the kitchen or another location without assistance, she has slight difficulty in orienting herself.		If the girl is asked to look at or go to the kitchen or another location without assistance, she often has difficulty in orienting herself.		If the girl is asked to look at or go to the kitchen or another location without assistance, she cannot orient herself.

III. . Temporal orientation:

1	1.5	2	2.5	3	3.5	4
If the word “later” is said to the girl, she understands that she has to wait.		If the word “later” is said to the girl, she sometimes understands that she has to wait.		If the word “later” is said to the girl, she hardly ever understands that she has to wait.		If the word “later” is said to the girl, she never understands that she has to wait.

IV. Memory:

1	1.5	2	2.5	3	3.5	4
The girl accurately remembers places and people she has already met, recognising them by smiling.		The girl does not always accurately remember places and the people she has already met, recognising them by smiling.		The girl hardly ever accurately remembers places and the people she has already met, recognising them by smiling.		The girl never remembers places and the people she has already met, recognising them by smiling.

V. Eye contact, replying by smiling, shared attention:

1	1.5	2	2.5	3	3.5	4
The girl has not difficulty in sharing attention, spontaneously looks for attention from adults and smiles when cuddled.		The girl sometimes has difficulty in establishing and maintaining spontaneous eye contact, smiling when cuddled or in the presence of social stimulus and sharing attention.		The girl often has difficulty in establishing and maintaining spontaneous eye contact, smiling when cuddled or in the presence of social stimulus and sharing attention.		The girl never establishes spontaneous eye contact, never responds to cuddling or social stimulus by smiling and never shares attention.

VI. Verbal communication:

1	1.5	2	2.5	3	3.5	4
The girl show intention in verbal communications; she manages to express her needs using sounds or short words.		The girl only sometimes manages to express her needs using sounds or short words.		The girl hardly ever manages to express her needs using sounds or short words.		The girl never communicates verbally in any way.

VII. Non-verbal communication:

1	1.5	2	2.5	3	3.5	4
The girl normally uses non-verbal communication; she knows how to express herself using gestures and facial expressions.		The girl has difficulty in non-verbal communication; she manages to point and reach out to what she wants with her hand but only inaccurately.		The girl manages to point and reach out to what she wants only inaccurately and only sometimes.		The girl generally cannot express her needs or wishes in a non-verbal manner.

SENSORAL AREA

VIII. Eyesight:

1	1.5	2	2.5	3	3.5	4
Visual response is in the norm with respect to age and is used as a means of exploring new objects and there is a fixed look towards objects.		Visual response is not within the norm with respect to age; it is not always used as a means of exploring new objects and there is not always a fixed look towards objects.		The girl uses an intermittent and peripheral look (does not look directly at objects, but does so from out of the corner of the eye), recognising the difference between known and unknown objects.		The girl seems not to recognise the difference between known and unknown objects when looking at them.

IX. Hearing:

1	1.5	2	2.5	3	3.5	4
Hearing response is in the norm with respect to age and is used as a means of exploring the surrounds.		Hearing response is not in the norm with respect to age and is not always used as a means of exploring the surrounds.		Hearing response varies; the girl alternates periods of hypersensitive hearing with moments of very low hearing (she recognises aural stimulus as being very strong or not at all).		The girl has an excessive or no reaction to sounds, independently of their type.

MOTORIAL AREA

X. Body:

1	1.5	2	2.5	3	3.5	4
The girl is able to maintain an erect position and to walk by herself. She knows how to look where she is going, walk on any surface and go up and down stairs.		The girl is able to maintain an erect position but sometimes needs support when walking.		The girl is able to maintain an erect position but always needs support when walking.		The girl is unable to maintain an erect position or walk by herself. She needs a wheelchair or a pram in order to move around.

XI. Hands:

1	1.5	2	2.5	3	3.5	4
Functional use of the hands is only slightly affected; the girl manages to grip and hold objects for long enough to enable her to make ample movements. She has good hand-eye coordination. Stereotypes to not influence the intentional use of the hands.		Functional use of the hands is more compromised; the girl manages to touch, push or hit objects but not to grip them. Hand-eye coordination is scarce. The girl is inhibited in moving by stereotypes.		Functional use of the hands is compromised; the girl is not always able to use her hands intentionally; she does not always manage to touch objects, even if strongly motivated to do so, especially in the presence of marked stereotypes.		Functional use of the hands is almost completely compromised; the girl is not able to use her hands intentionally; she does not manage to touch objects even if strongly motivated to do so, especially because of insistent stereotypes.

XII. Scoliosis:

1	1.5	2	2.5	3	3.5	4
The girl shows no signs of scoliosis.		The girl shows signs of minor scoliosis.		The girl shows signs of major scoliosis.		The girl shows signs of very serious scoliosis.

XIII. Feet:

1	1.5	2	2.5	3	3.5	4
The girl has no problems with her feet.		The girl has slightly small feet, with minor circulation problems.		The girl has small, valgus or different sized feet, with circulation problems.		The girl has problems with her feet, to the extent that she is unable to walk.

BASIC EMOTIONS

XIV. Basic emotions:

1	1.5	2	2.5	3	3.5	4
The girl has no difficulty in expressing her basic emotions (happiness, anger, fear, sadness) through visual expressions, body language and emotive expressions.		The girl has some difficulty in expressing her basic emotions (happiness, anger, fear, sadness) through visual expressions, body language and emotive expressions.		The girl has major difficulty in expressing her basic emotions (happiness, anger, fear, sadness) through visual expressions, body language and emotive expressions.		The girl is unable to express her emotions.

XV. Others emotions:

1	1.5	2	2.5	3	3.5	4
The girl has no difficulty in understanding others emotions.		The girl has some difficulty in understanding others emotions.		The girl has major difficulty in understanding others emotions.		The girl is unable to understand others emotions.

AUTONOMY

XVI. Control of the sphincter:

1	1.5	2	2.5	3	3.5	4
The girl has full control of her excretive functions.		The girl is not always able to control her excretive functions.		The girl only has part control of her excretive functions; she needs help.		The girl has no control of her excretive functions.

XVII. Feeding:

1	1.5	2	2.5	3	3.5	4
The girl eats and drinks by herself.		The girl has some difficulty in eating and drinking by herself.		The girl needs a little help in eating and drinking.		The girl is unable to eat and drink by herself; she needs to be fed.

XVIII. Ability to wash and dress:

1	1.5	2	2.5	3	3.5	4
The girl is able to wash and dress by herself.		The girl has some difficulty in washing and dressing.		The girl needs a little help washing and dressing.		The girl needs to be washed and dressed.

CHARACTERISTICS OF RETT SYNDROME

XIX. Mood changes:

1	1.5	2	2.5	3	3.5	4
The girl has no mood changes.		The girl sometimes has mood changes.		The girl often has mood changes.		The girl always has mood changes.

XX. Convulsions:

1	1.5	2	2.5	3	3.5	4
The girl does not have convulsions.		The girl sometimes has convulsions.		The girl often has convulsions.		The girl very often has convulsions.

XXI. Breathing problems:

1	1.5	2	2.5	3	3.5	4
The girl does not have breathing difficulties characterised by changes in breathing rhythm and frequency.		The girl sometimes has breathing difficulties characterised by changes in breathing rhythm and frequency.		The girl often has breathing difficulties characterised by changes in breathing rhythm and frequency.		The girl very often has breathing difficulties characterised by changes in breathing rhythm and frequency.

XXII. Hyperactivity:

1	1.5	2	2.5	3	3.5	4
The girl does not behave worryingly or impulsively.		The girl sometimes behaves worryingly or impulsively.		The girl often behaves worryingly or impulsively.		The girl always behaves worryingly or impulsively.

XXIII. Anxiety:

1	1.5	2	2.5	3	3.5	4
The girl does not have anxiety attacks.		The girl sometimes has anxiety attacks.		The girl often has anxiety attacks.		The girl always has anxiety attacks.

XXIV. Aggressiveness:

1	1.5	2	2.5	3	3.5	4
The girl does not show any aggression.		The girl is sometimes aggressive.		The girl is often aggressive.		The girl is always aggressive.

XXV. Bruxism:

1	1.5	2	2.5	3	3.5	4
The girl never gnashes her teeth.		The girl sometimes gnashes her teeth.		The girl often gnashes her teeth.		The girl always gnashes her teeth.

XXVI. Rolling of the eyes:

1	1.5	2	2.5	3	3.5	4
The girl never rolls her eyes towards each other.		The girl sometimes rolls her eyes towards each other.		The girl often rolls her eyes towards each other.		The girl always rolls her eyes towards each other.

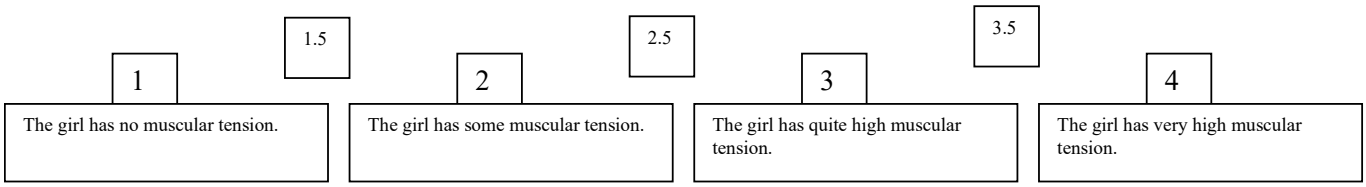
XXVII. Epilepsy:

1	1.5	2	2.5	3	3.5	4
The girl never has epileptic fits.		The girl sometimes has epileptic fits.		The girl often has epileptic fits.		The girl very often has epileptic fits.

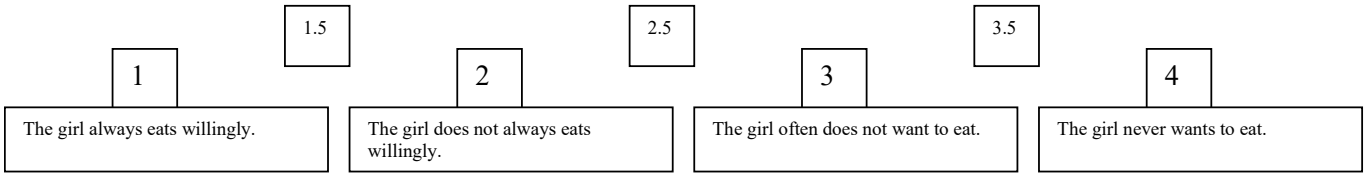
XXVIII. Aerophagia:

1	1.5	2	2.5	3	3.5	4
The girl does not suffer from aerophagia or intestinal problems.		The girl sometimes suffers from aerophagia or intestinal problems.		The girl often suffers from aerophagia or intestinal problems.		The girl very often suffers from aerophagia or intestinal problems.

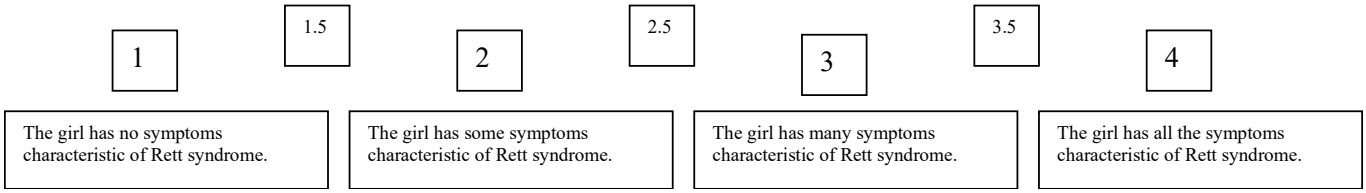
XXIX. Muscular tension:



XXX. Feeding habits:



XXXI. Overall impression:



Appendix 6 – Rett Syndrome Motor Evaluation Scale (RESMES)

	Item	Item definitions	Score	Comments
	Standing	The patient should stand on the floor (avoid soft surfaces) without external support for as long as possible. Score as follow: 0 = >60s; 1 = 30-60s; 2 = 10-29s; 3 = <10s; 4 = Impossible.		
Standing position	Independent	The standing position should be maintained without any external support.		
	Single support	The standing position should be maintained with one single support. Support should be provided with one hand to the patient's hand or wrist (not to the elbow or shoulder).		
	Double support	The standing position should be maintained with double support. Support should be provided with two hands to the patient's hands or wrists (not the elbows or shoulders).		
	Sitting	The patient should sit as long as she can. Do not use chairs with backrests. Score as follow: 0 = >60s; 1 = 30-60s; 2 = 10-29s; 3 = <10s; 4 = Impossible.		
Sitting position	On a stool without feet support	The patient should sit on a stool without back support and feet raised from the floor. 0 = the patient can maintain the position easily and indefinitely. 4 = The patient needs any kind of support (also minimal) to maintain the position.		
	On a stool with feet on the floor	The patient should sit on a stool without back support and feet on the floor. 0 = the patient can maintain the position easily and indefinitely. 4 = The patient needs any kind of support (also minimal) to maintain the position.		
	On the floor	The patient should sit on the floor. Legs could be crossed or extended based on which is easier for the patient. 0 = the patient can maintain the position easily and indefinitely. 4 = The patient needs any kind of support (also minimal) to maintain the position.		

	Postural change	Score as follow: 0 = Yes, independently, always, without external support; 1 = Yes, independently but leaning on supports (e.g., furniture); 2 = Yes, with the help of one person; 3 = NO, but if passively placed in the position, it can be maintained; 4 = NO and, if passively placed in the position, it can't be maintained.		
Postural changes	Rolling supine to side	0 = The rolling is possible independently and frequently when the patient is lying on her back without help or encouragement. 1 = The independent rolling is not frequently observed, but it is referred that the patient left supine was sometimes found on the side. 2 = help is intended as a person who initiates the patient's rolling movement by rotating a shoulder or moving an arm or a leg toward the rolling side.		
	Rolling supine to prone	0 = the rolling is possible independently and frequently when the child is lying on her back and if it happens without help or encouragement. 1 = the independent rolling is not frequently observed, but it is referred that the patient left supine was sometimes found on the stomach. 2 = help is intended as a person who initiates the patient's rolling movement by rotating a shoulder or moving an arm or a leg toward the rolling side.		
	From supine to sitting position	The patient can use the floor as a support base. Moreover, a stick can be placed next to the child (on the right or left side, indifferently – stick diameter: 2,5 cm). The patient can hold the stick to perform the task (score = 2). 0 = Yes, she usually sits from a supine position alone without pushing on her upper limbs to complete the position change; 1 = Yes, putting one or two elbows on the ground, but without leaning on persons or supports or passing through the side or prone position and then to a sitting position. 2 = help is intended as one adult's hand support or leaning on the stick. The adult can exert little traction and stabilize the balance but does not have to pull the patient to a sitting position or use two hands. 3 = No, but if passively seated from the supine position, she can remain seated for at least15 sec; 4 = NO, and if passively seated from the supine position, she can't maintain the sitting position.		
	From sitting on the floor to a standing position	The patient can use the floor as a support base. Moreover, a stick can be placed next to the child (on the right or left side, indifferently – stick diameter: 2,5 cm). The patient can hold the stick to perform the task (score = 1).		

		0 = Yes, she usually stands up from sitting on the floor alone without any support. 1 = Yes, with any kind of support (e.g., floor, stick, or furniture), but without the help of a person. 2 = help is intended as one adult's hand support. The adult can exert little traction and stabilize the balance but does not have to pull the patient to a standing position or use two hands.		
	From sitting on a chair to a standing position	The patient can use the armrests as support. Moreover, a stick can be placed next to the child (on the right or left side, indifferently – stick diameter: 2,5 cm). The patient can hold the stick to perform the task (score = 1). 0 = Yes, she usually stands up from sitting on a chair, alone, without any kind of support. 1 = Yes, with any kind of support (e.g., Stick or armrests), but without the help from a person. 2 = help is intended as one adult's hand support. The adult can exert little traction and stabilize the balance but does not have to pull the patient to a standing position or use two hands.		
	From standing to sitting on the floor	0 = Yes, she usually sits on the floor from the standing position, alone, without any kind of support. 1 = Yes, with any kind of support (e.g., furniture), but without the help from a person. 2 = help is intended as one adult's hand support. The adult can slightly push the patient and stabilize the balance but does not have to push the patient to a sitting position strongly or use two hands.		
	From standing to sitting on a chair	0 = Yes, she usually sits on a chair from the standing position, alone, without any kind of support. 1 = Yes, with any kind of support (e.g., Furniture or armrests), but without the help from a person. 2 = help is intended as one adult's hand support. The adult can slightly push the patient and stabilize the balance but does not have to strongly push the patient to sit on a chair position or use two hands.		
	Walking	The test can be performed with shoes and any lower limbs aid usually used by the patient. Let the patient walks straight on a long enough pathway with a regular floor (avoid soft surface). Report the gait characteristics in the note. Score as follow: 0 = >11 passi; 1 = <10 passi; 2 = NON eseguibile.		

Walking	Independent	If the patient needs any kind of support to walk, score = 2		
	Single support	Support should be provided with one hand to the patient's hand or wrist (not to the elbow or shoulder).		
	Double support	Support should be provided with two hands to the patient's hands or wrists (not the elbows or shoulders).		
	Step over obstacles	The test can be performed with shoes and any lower limbs aid usually used by the patient on a regular floor. Obstacles should be sticks (3 cm diameter) placed on the floor. The double obstacles are two sticks placed with 3 mt distance between each other. Score as follow: 0 = Yes: the obstacle overcoming is not casual; the patient does not touch the obstacle for at least three attempts on five; 1 = Sometimes: the patient goes over the obstacle slightly touching it or exploring the obstacle with the foot before overcoming it at least one attempt out of five. 2 = No: the patient never overcame the obstacle in any of the five attempts.		
Step over a single	Independent	The patient should overcome the obstacle without any external support.		
	Single support	Support should be provided with one hand to the patient's hand or wrist (not to the elbow or shoulder).		
	Double support	Support should be provided with two hands to the patient's hands or wrists (not the elbows or shoulders).		
Step over a double	Independent	The patient should overcome the obstacles without any external support.		
	Single support	Support should be provided with one hand to the patient's hand or wrist (not to the elbow or shoulder).		
	Double support	Support should be provided with two hands to the patient's hands or wrists (not the elbows or shoulders).		
Runs	**Runs**	Run is intended as a faster walking with a phase in which both feet are in the air. Support should be provided to the patient's hands or wrists (not to the elbow or shoulder). Score as follow: 0 = Always possible and independent; 1 = Possible independently at intervals (at least three consecutive steps without double support); 2 = Possible with single support (at least three consecutive steps without double support); 3 = Possible with double support (at least three consecutive steps without double support); 4 = Not possible.		

	Stairs	Support should be provided to the patient's hands or wrists (not to the elbow or shoulder). Score as follow: 0 = The patient goes up / down the stairs independently, without holding the handrail, and with one foot for each step. 1 = The patient climbs / descends the stairs with or without one foot for each step or holding the handrail, but without the help of a person. 2 = The patient climbs / descends one or more steps with or without one foot for each step and with unilateral support provided by a person; 3 = The patient climbs / descends one or more steps with both feet for each step with bilateral support by a person; 4 = The patient cannot climb stairs even with support.		
Stairs	Upstairs	Observe the patient going up a whole flight of stairs.		
	Downstairs	Observe the patient going down a whole flight of stairs.		
Total score:				

Appendix 7 - Rett Syndrome Behavior Questionnaire (RSBQ)

For each characteristic LISTED BELOW, please think about whether or not it accurately describes your daughter at this very point in time.

- For those VERY TRUE characteristics OR OFTEN TRUE, please tick box 2.
- For those SOMEWHAT OR SOMETIMES TRUE characteristics, please tick box 1.
- If the behavior DOES NOT describe your daughter, please tick box 0 to indicate that the behavior is NOT TRUE AS FAR AS YOU KNOW.

Example

If your daughter uses gesturing very frequently to obtain desired objects, you will tick box 2 to indicate that it is very true or often true:

0	1	√ 2

0	1	2	1. She screams hysterically for long periods of time and cannot be consoled.
0	1	2	2. Although she can stand independently, she tends to lean on objects or people. (*If your daughter does not stand, please leave blank)*
0	1	2	3. Restricted patterns of hand movement.
0	1	2	4. The abdomen fills with air and sometimes feels hard.
0	1	2	5. Spells of laughter for no apparent reason during the day.
0	1	2	6. She has wounds on her hands as a result of repetitive hand movements.
0	1	2	7. She makes mouth grimaces.
0	1	2	8. There are times when she is irritable for no apparent reason.
0	1	2	9. Spells of inconsolable crying for no apparent reason during the day.
0	1	2	10. She uses eye gaze to convey feelings, needs, and wishes.
0	1	2	11. She makes repetitive tongue movements.
0	1	2	12. She rocks herself when her hands are prevented from moving.

0	1	2	13. She makes grimacing expressions on her face.
0	1	2	14. She has difficulty breaking/stopping repetitive hand movements.
0	1	2	15. She vocalizes for no apparent reason.
0	1	2	16. Spells of laughter for no apparent reason during the night.
0	1	2	17. Spells of apparent panic.
0	1	2	18. She walks with stiff legs. *(If your daughter does not walk, please leave blank)*
0	1	2	19. She tends to bring her hands together in front of her chin or chest.
0	1	2	20. Rocks body repeatedly.
0	1	2	21. The amount of time spent looking at objects is longer than the time spent holding or manipulating them. *(If your daughter doesn't hold/manipulate objects, leave blank)*
0	1	2	22. Spells of inconsolable crying for no apparent reason during the night.
0	1	2	23. She appears isolated.
0	1	2	24. She makes repetitive hand movements involving fingers around the tongue.
0	1	2	25. Grinds teeth.
0	1	2	26. Vacant 'staring' spells
0	1	2	27. There are times when breathing is deep and fast (hyperventilation).
0	1	2	28. Spells of screaming for no apparent reason during the day.
0	1	2	29. She makes repetitive hand movements with her hands apart.
0	1	2	30. There are times when the breath is held.
0	1	2	31. Air or saliva is expelled from the mouth with force.
0	1	2	32. Spells of apparent anxiety/fear in unfamiliar situations.
0	1	2	33. She seems frightened when there are sudden changes in her body position.
0	1	2	34. There are times when parts of the body are held rigid.

0	1	2	35. She shifts her gaze with a slow horizontal turn of the head.
0	1	2	36. She has an expressionless face.
0	1	2	37. Spells of screaming for no apparent reason during the night.
0	1	2	38. She presents abrupt mood changes.
0	1	2	39. There are certain days/periods where she performs much worse than usual.
0	1	2	40. There are times when she appears miserable for no apparent reason.
0	1	2	41. She seems to look through people into the distance.
0	1	2	42. She does not use her hands for purposeful grasping.
0	1	2	43. She swallows air.
0	1	2	44. Her hand movements are uniform and monotonous.
0	1	2	45. She has frequent naps during the day.