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Original Research

Impact of a 12-month multifaceted neurological physiotherapy intervention on gross motor function in women with Rett syndrome

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Abstract

Background: Rett syndrome is a rare genetic neurological syndrome that affects mostly females. The syndrome leads to severe impairments impacting all areas of the affected persons' life, including speech, mobility, eating, and breathing impairments. The most distinct symptoms include stereotyped hand movements, ataxia, and atrophy of the lower limbs, and signs of autism. **Methods**: According to the principle of convenience sampling, the quantitative research included five females diagnosed with Rett syndrome subject to their personalized goal oriented neurological physiotherapy. Changes in gross motor function were assessed by the Gross Motor Function Measure 88 and Rett syndrome Gross Motor Scale. **Results**: It was found that the 12-month multifaceted neurological physiotherapy intervention had statistically significant improvements in both Gross Motor Function Measure 88 ($p = 0.005$) and Rett syndrome Gross Motor Scale ($p = 0.012$). Despite positive improvements, the absence of control group made it difficult for a comparative evaluation to determine what interventions had the best possible outcomes. **Conclusions**: The quantitative research demonstrates neuro-developmental treatment sessions, hippotherapy, hydrotherapy, physical therapy, a walking program, endurance exercises, active-assisted exercises, and coordination exercises, had a significant impact on improving gross motor function status. Current multifaceted intervention program leads to good improvement of gross motor skills above what can be expected from late motor deterioration.

Keywords: Rett syndrome; Gross motor function; Neurological physiotherapy; Genetic neurological disorder; Habilitation; MECP2

1. Introduction

The European Union categorizes rare diseases as the ones which prevalence does not exceed 5 per 10.000 persons [1]. This includes also the Rett syndrome (RTT). RTT is a rare and complex genetic based progressive neurodevelopmental disorder, which emerges mostly in females and has no visible symptomatology before 6–18 months of age [2–7]. RTT leads to severe deteriorations and impairments affecting a wide range of persons' life through the lifespan. Impairments include atypical motor and respiratory function and challenging inability to speak and feed [4,5,8]. The syndrome is regardless of race and other demographic features [2–4]. Its epidemiology varies and includes values from 1:10.000 [9], 1:12.000 [10], 1:15.000 [11] to 1:25.000 [12] new-born females. Slovenia is also not exempt with the low incidence. According to the Department of Child, Adolescent & Developmental Neurology, University Children's Hospital Ljubljana, Slovenia has 18 active female cases of RTT.

RTT is nowadays considered as a neurological and neuro-developmental disorder, and also a part of a spectrum of diseases related to a mutation of the methyl CpG binding protein 2 (MECP2) gene, which is located on the long arm (q) of the X chromosome (Xq28). TheMECP2 gene codes for a protein that may downregulate the activity of many other genes. Therefore, mutations in MECP2 gene leads to defective epigenetic regulatory molecules [5,7,13–15].

RTT is confirmed and diagnosed based on diagnostic criteria and genetic testing [16]. However, genetic testing is not appropriate for every case. Studies show that 3–5% [17] and 5–10% [12] of RTT cases do not involve the MECP2 mutation. In such cases the diagnostic procedure follows clinical criteria. The latest criteria were established, modified, and approved in 2001 by the European Pediatric Association [12,18]. Four main and eleven supportive criteria designate the presence of RTT diagnosis. Clinical features include also behavioral and motor regression. Normal/typical RTT is defined on four main criteria, whereas atypical RTT (consists of five types of RTT: (1) Early-onset seizure type; (2) Congenital variant; (3) Forme fruste variant; (4) Late childhood regression variant; (5) Preserved speech variant) is considered when an individual attains at least two main criteria and at least five supportive criteria [2–4,17]. Main criteria incorporate (1) partial or complete loss of acquired purposeful hand skills; (2) partial or complete loss of spoken language; (3) gait abnormalities (impaired or absence of ability); (4) stereotypic hand movements such as hand wringing/squeezing, clapping/tapping,

mouthing, and washing/rubbing automatisms. Supportive criteria incorporate: (1) bruxism while awake; (2) impaired sleep; (3) abnormal muscle tone; (4) peripheral vasomotor disturbances; (5) scoliosis/kyphosis; (6) growth retardation; (7) small cold hands and feet; (8) inappropriate laughing/screaming spells; (9) diminished response to pain; (10) intense eye communication (»eye pointing«) [2–4,17].

Manifestation of RTT includes four stages of development with profound phenotypic features commencing with deteriorations in already achieved functions [4,5]. Stages arise in between 6 months of age and >10 years of age [5]. The decrease in gross motor function is one of the first deteriorations present in assumption off RTT [2,3]. Stereotypical hand movement, regression in gross motor function, microcephaly, epilepsy, regression in postural reactions (righting, protective and equilibrium reactions), spasticity, hypersensitivity, bradykinesia, dystonia, ataxia, apraxia, tremor, cardiac dysfunction, and postural impairments are some of the most common phenotypic RTT features/comorbidities [3–6,19–23]. Correlation between phenotype and genotype is in the mutation type [5,7]. Several different types have been recognized so far, whereas an Australian study in 2011 determined types p.R106W, p.R133C, p.T158M, p.R168X, p.R255X, p.R270X, p.R294X, p.R306C to be the most common into having a connection to pathogenic MECP2 mutation [5].

Due to complexity and severity of impairments, progressive-regressive developmental combination, incidence of deformities, and limitations through individuals' lifespan, RTT requires a wide range of interventions [24,25]. Inspection, evaluation and (re)habilitation procedures require both medical approaches — interdisciplinary (regarding comorbidities) and multidisciplinary (regarding lifelong management) [4,26]. Similar findings regarding importance and urgency of a multidisciplinary team across the lifespan were also recognized by other authors [4,11, 16,24,25]. Multidisciplinary management of RTT across the lifespan is required due to the multisystem comorbidities found in RTT [25]. Neurological physiotherapy (neurophysiotherapy) intervention is one of several interventions required throughout the lifespan of an individual with RTT.

Neurophysiotherapy intervention is based on mitigating/resolving impairments in achieving typical development goals, preserving, and improving motor skills, preserving, and developing existing transitional skills, preventing, and reducing deformities, alleviate discomfort, and improving independence [4]. The purpose of the intervention is therefore based on the development of activity-related goals, activity-focused intervention, and impact-focused intervention [27]. Maintain existing gross muscle strength, maintain mobility of the lower and upper extremities, maintain existing ability to walk and improve existing gross motor function are the main purposes of the neurophysiotherapy intervention [4,8,27–30]. Due to the type of MECP2 mutation resulting in variability of already achieved developmental stages, the exact onset of neurophysiotherapy (re)habilitation cannot be determined. Thorough inspection and evaluation, with excellent knowledge of the pathogenesis and criteria of RTT, is of utmost importance.

By improving gross motor function, a beneficial affect was recognized in fine motor functions/skills, grasp duration, stereotypy reduction and finger feeding abilities. Furthermore, a few additional studies reported increased happiness, sociability, and reduced anxiety. Beneficial results are also seen in eye gaze regarding hydrotherapy targeting movement [27,30–34].

Till now several different approaches have been used on individuals with RTT, to improve the quality of their life. The wide range of such approaches include traditional, innovative, and alternative physiotherapy, which all had beneficial results on patients. However, due to the lack of research evidence, no approach can be recommended over another, which emphasized the multifaceted interventions. Furthermore, early developmental intervention is still necessary, to reach the full potential of the female with RTT, as also individualized physical therapy programs to consequently receive the most appropriate treatment. An involvement of individuals' family or caregivers is necessary in each interventional program. In the future researchers must focus on the methodology and higher level of relevant evidence to back up the existing results [4,11,24].

As clinical research in neurophysiotherapy in persons with RTT faces several barriers that comprise the difficulty to recruit participants with RTT due of rarity, there is limited knowledge regarding: (1) evidence-based physiotherapy intervention strategies in RTT; (2) limited knowledge on natural history and development over time; (3) difficulties choosing clinically relevant outcome measures in gross motor function.

The purpose of this multiple case study is to introduce our interdisciplinary 12–month consistent multifaceted neurological physiotherapy intervention (MNPTI) by finding a minimal clinically important difference in gross motor function of five females with RTT demonstrated with statistical results of the Gross Motor Function Measure 88 (GMFM-88) and the Rett syndrome Gross Motor Scale (RSGMS).

2. Materials and methods

In this multiple case study research, the impact of a 12-month MNPTI on gross motor function in females with RTT was studied. Within the study carried out in 2018 we evaluated five females (convenience sample) aged between 17 and 44 (Mean = 28) diagnosed with RTT who participated in a 12-month habilitation intervention (Table 1). The intervention consisted of six to eight neurological physiotherapy interventions aimed to improve gross motor function (Appendix). Females were evaluated pre- and -post intervention using GMFM-88, which is used for most individuals with developmental disorders including RTT [35], and RS-

Table 1. 12–month multifaceted neurological physiotherapy intervention.

Intervention frequencies by birth year of females with RTT								
Birth year	Neuro-developmental therapy	Hippotherapy	Hydrotherapy	Task oriented exercise training	Walking program	Endurance program	Active-assisted exercise	Coordination exercise
1974	daily	1–2 per week	weekly	none	daily	weekly	daily	daily
1991	daily	1–2 per week	weekly	none	daily	weekly	daily	daily
1991	daily	none	weekly	weekly	daily	weekly	daily	daily
1993	daily	none	weekly	none	daily	weekly	daily	daily
2001	daily	1–2 per week	weekly	none	daily	weekly	daily	daily

Table 2. Gross motor function measure 88 evaluation with significance.

GMFM-88 dimension	Evaluation time	Birth year of female with RTT and evaluated GMFM-88 scores					*p*
		1993	1991	1991	1974	2001	
A	Pre	54.90	5.88	64.70	54.90	50.98	0.003
	Post	96.07	25.49	84.31	78.43	76.47	
B	Pre	85.00	8.33	58.33	21.67	35.00	0.017
	Post	96.67	61.66	90.00	38.33	63.33	
C	Pre	52.38	7.14	4.76	0.00	2.38	0.032
	Post	88.09	61.90	95.23	2.38	50.00	
D	Pre	61.50	7.69	30.77	2.56	5.12	0.019
	Post	89.74	38.46	92.30	10.25	43.59	
E	Pre	38.88	6.94	20.83	11.11	6.94	0.012
	Post	68.05	16.67	55.55	22.22	30.55	
Total	Pre	58.53	7.19	35.87	18.04	20.08	0.005
	Post	87.72	40.83	83.47	30.32	52.78	

GMS, purposefully used for persons with RTT [13]. Due to RSGMS not yet validated in Slovenia, same results from GMFM-88 were transferred to RSGMS to increase validity. The small sample size in this study is due to a low incidence of RTT in Slovenia. Consequently, establishing a control group in this study was made impossible. Such absence led to an incomparable evaluation to determine what interventions had the best possible outcome. Current national data in the Department of Child, Adolescent & Developmental Neurology, University Children's Hospital Ljubljana, obtained in January 2021, reports 18 cases of RTT in Slovenia.

GMFM-88 consists of five dimensions in gross motor function (A: lying and rolling; B: sitting; C: crawling and kneeling; D: standing; E: walking, running, and jumping) assessed with scoring key from 0–3 (0 = does not initiate; 1 = initiates; 2 = partially completes; 3 = completes). Evaluation is in percentage.

RSGMS consists of three subscales (1. sitting subscale; 2. standing and walking subscale; 3. challenge subscale) assessed with scores from 0–3 (0 = maximal, 1 = moderate, 2 = minimal; 3 = none). Maximal score is 45.

The study was carried out by the principles of International Code of Medical Ethics and the Helsinki/Tokyo Declaration. We also obtained the consensus of the Commission of the Republic of Slovenia for medical ethics (no. 0120-47/2018/4), as well as the consensus of RTT females' parents.

2.1 Statistical analysis

Data were statistically processed using the IBM SPSS Statistics 25 software (SPSS Inc., Chicago, IL, USA) and presented with table demonstrations. Statistical feature was tested on 5% risk level ($p = 0.05$). Kolmogorov-Smirnov and Shapiro-Wilk test was used for verification of normal distribution of variables between the approximate locomotor ability of females pre and post habilitation. Paired *t*-test was used for equality of means within pre and post habilitation of females with RTT.

3. Results

In this study, five females with diagnosed RTT, aged between 20 and 47 (Mean = 31), were subjected to a 12-month MNPTI and evaluated by the means of GMFM-88 and RSGMS. Several statistically significant improvements have been found. GMFM-88 evaluation (Table 2) presents gross motor activities in five different dimensions. Statistically significant improvements of gross motor function have been recognized in all five dimensions within all five females with RTT (A: $p = 0.003$; B: $p = 0.017$; C: $p = 0.032$; D: $p = 0.019$, E: $p = 0.012$). Difference (Table 3) between total score pre-intervention (Mean = 27.94%) and

Table 3. Mean of gross motor function measure 88 score with significance and confidence interval.

	Mean of GMFM-88 evaluation score pre-intervention	Mean of GMFM-88 evaluation score post-intervention
	27.94	59.02
p	0.005	
95% confidence interval	Lower bound 46.78% Upper bound 15.39%	

Table 4. Rett syndrome gross motor score evaluation with significance.

RSGMS	Evaluation	Birth year of female with RTT and evaluated RSGMS					*p*
Subscale with total score	time	1993	1991	1991	1974	2001	
Sitting (9)	Pre	4	0	5	0	2	0.025
	Post	7	3	8	3	5	
Standing and Walking (27)	Pre	7	0	3	0	1	0.027
	Post	15	3	17	4	6	
Challenge (9)	Pre	0	0	0	0	0	0.178
	Post	2	0	2	0	0	
Total (45)	Pre	11	0	8	0	3	0.012
	Post	24	6	27	7	11	

Table 5. Sum of Rett syndrome gross motor scale score with significance and confidence interval.

	Sum of RSGMS evaluation score pre-intervention	Sum of RSGMS evaluation score post-intervention
	22	75
p	0.012	
95% confidence interval	Lower bound 17.32% Upper bound 3.88%	

total score post-intervention (Mean = 59.02%) is 31.08%. The average total improvement of five females in GMFM-88, with a standard deviation of 12.64%, is 31.08%. With a certainty of 95%, we confirm that the 12-month multifaced neurophysiotherapy intervention had statistically significant improvements in gross motor function within all five females with improvements between 15.39% and 46.78% and significance of $p = 0.005$. Improvements are also statistically significant in the RSGMS evaluation (Table 4 and Table 5). It was found that the MNPTI had a significant impact ($p = 0.012$) on improved gross motor function within all five females with RTT. The average total improvement in gross motor function in all five females with RTT in RSGMS is with 95% certainty between 3.88 and 17.32. Statistically significant improvements were found in all three subscales (Sitting: $p = 0{,}025$; Standing and Walking: $p = 0.027$; Challenge: $p = 0.178$).

4. Discussion

Neurological physiotherapy interventions are based on achieving realistic developmental goals, maintaining and improving motor skills, developing or maintaining the existing ability to transfer, decreasing or preventing deformities, easing discomfort or irritability, and improving the level of independence [4]. The purpose of the intervention is therefore to develop activity-related goals, activity-focused and impairment-focused intervention [27,28]. With this, we wish to improve the existing gross muscle strength, maintain the flexibility of upper and lower extremities, the existing ability to walk, and improve the existing gross motor function [4,8,27–30]. Evaluating patients' conditions and monitoring improvements/deteriorations within the intervention is highly important [31]. The fundamental purpose of medical scores is to determine decision-making, clinical decisions, and clinical management in a patients' intervention process [32]. Scores are needed to be based on easily recordable variables, well-calibrated, have a high level of discrimination, should apply to all patient populations, could be used internationally, and would be able to predict a functional status or quality of life [31]. A Romanian study determined scores being increasingly efficient in patient management [32]. RTT involves a complex form of pathologies with a progressive-regressive combination and a high incidence of deformities [4]. Inspection, evaluation, and (re)habilitation procedures are thus significantly important and demand a wide spectrum of interventions [26].

Due to RTT limitations by atypical postural characteristics, reduced righting techniques, protective reactions, and equilibrium reactions, functional task limitation, motor learning difficulties, motor control limitations, poorer coordination, planned movement, stereotypical hand movement, spasticity and ambulatory, interventions towards im-

proving righting, balance, protective reactions and gross motor function is preferential due to the importance of upright position, postural control, and selective movement in everyday life [5,6,20,21].

This research introduces gross motor improvement in the 12-month multifaced neurophysiotherapy intervention consisting of six to eight neurophysiotherapy activities within five females with RTT. Basic physiotherapy practice (five exercises/programs) was improved by including neuro-developmental therapy (NDT), hippotherapy and hydrotherapy into the 12-month physiotherapy intervention. Activities were selected within the ability of the institution and up to date evidence-based practice. Several authors highlight lack of research in the field of physiotherapy in RTT, low incidence of strong research evidence, cross-comparative studies and therefore inability to favor any treatment plans or activities [11,24]. We found several positive implications within our study covered with GMFM-88 and RSGMS. Two recent (in 2020) systematic reviews on physiotherapy interventions made in Italy and Canada highlighted multifaced interventions as interventions providing good results within individuals with RTT [11] and positive effects of physiotherapy intervention aimed towards improving gross motor function [24]. In favor of gross motor function intervention, personalized physiotherapy improved comorbidities/developmental impairments regarding not only ambulation and transition movement, but also fine motor function, gross motor improvements in grasp duration and stereotypical hand movement reduction, and improved finger feeding ability were also obtained. Other implications consist of increased happiness and sociability with reduced anxiety, choice-making, and eye-pointing [24]. It was also found that all clinically meaningful improvements were induced by high-intensity interventions [4,24].

NDT reduces pathological activity and induces the development of normal motor patterns since it optimizes individuals' functions by improving body control, posture control, and selective movement [4,8]. NDT has multiple positive implications regarding the establishment of potential motor patterns in a form reachable for the individual [4,36]. Firstly, the intervention incorporates inhibiting motor patterns of the body and extremities', and later primary reflexes [36]. Facilitation techniques are also a part of NDT. The NDT facilitation techniques improved head and trunk control (which is foundational for the development of functional tasks) movement patterns, righting, balance and protective reactions, and weight-bearing of arms in females with RTT. Participants learned to perform new functional tasks and NDT handling was used as a form of feedback on their motor performance. The habilitation process was focused on movement and balance reactions to reduce worsening of impaired posture and motor dysfunction, irregular head positioning, and asymmetry of the thoracic spine as suggested by other authors [29,36,37]. Asymmetric posture is mostly formed by abnormal torso shape and induced by asymmetric motor patterns. One of several is also unilateral head rotation and lateral position of upper extremities [30]. Scoliosis and kyphosis appear due to the asymmetrical muscular tone and are predicted by scoliosis symptoms appearing before the age of five, when females were already hypotonic in their childhood and thus unable to walk, or were able to walk and later rapidly lost the ability [4,7,20].

Girls who experienced difficulties in development in their first 6 months after birth are more prone to the incidence of scoliosis by the age of 6 [20]. 61% of immobile patients and 25% of mobile patients require surgical correction of scoliosis [4,7,20]. Scoliosis progresses annually an average of 14 degrees [4,7,20]. Our research demonstrated that despite the annual regression, the lowest score during the assessment of sitting was not achieved by the oldest female, and similarly, the highest score was also not achieved by the youngest female. Sitting ability was prior the 12-month intervention limited. Females were unable to maintain their position due to minimally developed or undeveloped righting techniques. Several changes were found after 12-months of neurophysiotherapy intervention, whereas improvements included gained righting techniques, head control, and control over extremities while seated. One of several studies researching sitting abilities found that only one-third of girls with RTT can independently sit on the floor or in a chair/wheelchair [6].

Numerous improvements were also found in the gross motor function of children with Cerebral palsy [30]. It was discovered that three months of intensive NDT had positive statistically significant differences in functions as lying, sitting, crawling, and kneeling, as well as in the ability to stand [30]. The ability to stand and walk also depends on body coordination, where 50 to 85% of females with RTT master walking, some deprive this ability later throughout their regression develops, others are never able to master walking [4,27,32]. The extent of inability among females varies, some are incapable to independently rotate while standing, independently sit and independently transfer from floor to chair [4,38].

Hydrotherapy has been a huge beneficial impact on RTT by reducing spasticity, anxiety, hyperactive behavior and softening rigid tissues. The warm water, which is part of the therapy, triggers calmness in the individual that consequently has an impact on their sensory input [4,39,40]. The water can assist in active movement, promotes relaxation, strengthens muscle, and improves circulation. The fear of falling consequently disappears, as females can easily and freely move in the water without any hesitations. Furthermore, the pleasantness of achieving new limits can occur throughout several water activities, which can also enhance the lost or latent motor skills, due to mobility improvement in the water [41,42]. It also has a positive impact on stereotypical movements [39,40]. The study explains that after eight weeks of hydrotherapy improvements

in feeding activities, hand skills, balance and interactions with the environment were seen, which also has an impact on developing self-esteem, self-awareness, and a sense of accomplishment. Hydrotherapy is often used as a tool to learn correct breathing, head control, balance, relaxation, effective hand use, body movements including walking and social interactions [4,39,43].

Hippotherapy is used for treating a wide range of conditions in neurological, orthopedic, or psychological origin, and has a positive outcome on gross motor function and functional activities [22,44]. By using horses' movement to achieve improvement in neurological functions, sensorimotor processing, and motor integration, it covers fields of physiotherapy, occupational therapy, and speech therapy [30,45]. According to the presence of certain features of autism in females with RTT, the research showed a wide spectrum of enhancements on autism characteristics regarding improvements in social integration, bearing, and sensorimotor function [37,46]. Progress can also be furtherly confirmed, with studies presenting the use of hippotherapy within children with cerebral palsy and other neurological diseases, by positively affecting their righting functions and postural balance, therefore consequently allowing patients to achieve improved condition with regards to gross motor function and functional activity [22,47–49]. Recent studies define 10–12 hippotherapy sessions to be required for positively impacting postural characteristics [30,49]. Some individuals achieve significant progress at their first therapy session and others after 40 therapies [30].

In the first pilot study using randomized control study in subjects with RTT the authors researched the efficacy of NDT and hippotherapy on dynamic balance and gross motor function. Six females with RTT were randomized to the experimental (N = 3) and to the controlled group (N = 3). Subjects with RTT in the study group improved their average results in all gross motor function dimensions (A-lying and rolling, B-crawling and kneeling, C-siting, D-standing, E-walking, running and jumping) in comparison with subjects with RTT in control group. There were statistically significant differences ($p < 0.05$) in the GMFM-88 and Functional reach test results between the study and the control group, in favor of the study group [50].

Improvements in strength and range of motion were also identified, thus improvements of walking ability and improved static balance were also induced [44]. Improved activation of flexors and torso extensors improves gross motor function (specially in lying and turning) of an individual, whereas improvements are mostly preserved for only three weeks. This indicates hippotherapy to be a long-term habilitation intervention [29]. For preserving improvements achieved in posture by NDT and hippotherapy, therapeutic corsets are being implemented for limiting deteriorations and development of contractures [30]. Other studies also discovered similar findings [30,51–54]. There were statistically significant differences regarding turning, sitting, and kneeling [51], a complete improvement of the gross motor function [52], and improvement of functional movement [30].

In combination with NDT, hippotherapy and hydrotherapy, our neurophysiotherapy intervention consisted of five physiotherapy activities including: (1) task-oriented exercise training; (2) walking program; (3) endurance program (treadmill training and high intensity of exercise training); (4) active-assisted exercise; (5) coordination exercise (Appendix). The impact of the intervention is also recognized in other characteristics, such as vegetative and cognitive [27,29,51]. Various activities, such as task-oriented exercise training, walking and active exercises with passive stretching are part of every physiotherapy intervention [11,23,24]. Functional exercise has numerous positive effects on performance in daily activities and gross motor function [53]. Passive movement, active-assisted, and active exercises reduce regression, improve cardiac function, and contribute to the preservation of bone density [23,55]. Overall physical activity of females with RTT is beneficial in case of metabolic and cardiovascular insufficiency, mainly with regards to blood supply towards distal body areas and a lower resting heart rate [38]. Improvements in cardiovascular fitness and in functional ability under the influence of treadmill training was observed in four females with RTT in a study done in 2004 [38] and in 12 females with RTT with their positive autonomic respose in 2018 [56]. One individual also regained independent gait in a study from 2015 [57].

Our intervention generally presents progress in areas of impulsive stereotypical movements, head rotation, improved sitting position, improved righting technique (postural reactions), and easier manual actions. Motor learning reduced cognitive deficit which resulted in increased ability to focus and concentrate during physiotherapy activities, females became more perceptive of their surroundings, and less impulsive with reduced emotional outbursts. Positive effects of physical activity on disruptions in concentration were also demonstrated in other studies [4,57]. The latter has also been confirmed by studies, where a recent one demonstrated that individuals' manual activity can only be altered in a persistent environment enriched with motivation [19]. The more independent, the lesser the regression of manual skills [19]. In addition to improved gross motor function, our study ascertain reduce in frequency of stereotypical hand movement, reduced sensitivity to external factors, improved environment awareness and eye gaze, with incidence of laughter and occasional eye blinking.

Improvements of gross motor function status are possible under two conditions: (1) a continuous number of therapies; (2) Neuro physiotherapy specialists with specific skills regarding habilitation of RTT involving up-to-date evidence-based practices [29].

Limitations of the study

It is important to address the low incidence of RTT in Slovenia. According to the most recent data (January 2021), Slovenia has 18 registered cases of females with RTT, which are managed and monitored in several different institutions and therefore difficult to collaborate within the study interest of greater sample. Such epidemiology prevented to form a control group for the purpose of comparison. This could recognize which interventions had the greater positive impact. It is also important to highlight that the multifaceted neurological physiotherapy intervention was carried out by a team of professionals, whereas all participated females with RTT were not treated by the same professional in the given 12-months (they were randomly selected), also all of them did not receive all eight interventions due to their involvement in a pilot study. There is also no method to determine the relative positive impact of any of the individual interventions.

5. Conclusions

It was found that our 12-month MNPTI, consisting of eight different interventions: NDT, hippotherapy, hydrotherapy, task-oriented exercise training, walking program, endurance program, active-assisted exercise, and coordination exercise, statistically significantly improved the gross motor function status of five randomly selected females with RTT by the means of RSGMS and GMFM-88. It can be therefore recommended for neurorehabilitation specialists to consider such a combination of habilitation interventions in individuals with RTT, whereas new emerging entities are of utmost importance.

Abbreviations

RTT, Rett syndrome; MECP2, methyl CpG binding protein 2; MCID, minimal clinically important difference; MNPTI, multifaceted neurological physiotherapy intervention; GMFM-88, Gross Motor Function Measure 88; RSGMS, Rett syndrome Gross Motor Scale; NDT neurodevelopmental therapy.

Author contributions

AK, TK and TV conceived and designed the experiments; AK and TK performed the experiments; AK analyzed the data and wrote the manuscript, TK, NK and TV revised and approved the manuscript.

Ethics approval and consent to participate

The study was carried out by the principles of International Code of Medical Ethics and the Helsinki/Tokyo Declaration. We also obtained the consensus of the Commission of the Republic of Slovenia for medical ethics (no. 0120-47/2018/4), as well as the consensus of RTT womens' parents.

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Conflict of interest

The authors declare no conflict of interest. TV is serving as one of the Guest Editors of this journal. We declare that TV had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to RF.

Appendix

GOALS AND INTERVENTIONS WITHIN FEMALES WITH RTT

1. Female with RTT — 1. case (code ŽRS1)

Birth year: 1993

Physiotherapy goals:

- Maintains the ability to sit down independently from a lying position
- Preservation of existing scoliosis
- Improving gross motor function
- Maintaining the ability to walk to the first floor with assistance

Intervention:

- NDT,
- coordination exercise,
- hydrotherapy,
- active-assisted exercise,
- endurance program,
- walking program.

2. Female with RTT — 2. case (code ŽRS2)

Birth year: 1991

Physiotherapy goals:

- Maintaining existing gross muscle strength,
- maintaining mobility in the lower and upper extremities,
- maintaining existing walking ability,
- Improving gross motor function.

Intervention:

- NDT,
- Coordination exercise,
- hydrotherapy,
- hippotherapy,
- active-assisted exercise,
- endurance program,
- walking program.

3. Female with RTT — 3. case (code ŽRS3)

Birth year: 1991

Physiotherapy goals:

• Maintaining the ability to walk with the assistance of one person,

• maintaining existing gross muscle strength,

• Improving gross motor function.

Intervention:

• NDT,

• coordination exercise,

• hydrotherapy,

• active-assisted exercise,

• endurance program,

• walking program.

4. Female with RTT — 4. case (code ŽRS4)

Birth year: 1974

Physiotherapy goals:

• Maintaining existing gross muscle strength,

• maintaining the mobility of the lower and upper extremities,

• maintaining existing walking ability,

• Improving gross motor function.

Intervention:

• NDT,

• coordination exercise,

• hydrotherapy,

• hippotherapy,

• active-assisted exercise,

• endurance program,

• walking program.

5. Female with RTT — 5. case (code ŽRS5)

Birth year: 2001

Physiotherapy goals:

• Maintaining existing gross muscle strength,

• maintaining the mobility of the lower and upper extremities,

• maintaining existing walking ability,

• Improving gross motor function.

Intervention:

• NDT,

• coordination exercise,

• hydrotherapy,

• hippotherapy,

• active-assisted exercise,

• endurance program,

• walking program.

ACTIVITY TIME AND DESCRIPTION

NDT: 60 min

Hippotherapy: 30 min

Hydrotherapy: 60 min

Physical therapy (task-oriented exercise training to restore balance and gait): 60 min

Walking program: 30 min

Endurance program (treadmill training + high intensity of exercise training): 45 min

Active-assisted exercise: 30 min

Coordination exercises: 30 min

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