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Methodologies to objectively assess gait and postural control features in Rett syndrome – With a comment on specific challenges and how to address them

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ABSTRACT

Introduction. New pharmacological agents and behavioral interventions designed to ease key symptoms of individuals with Rett syndrome are currently emerging. To carefully evaluate these interventions in this complex and rare disorder, it is paramount to develop robust and objective measures which can be utilized and compared across clinics and research centers. The ability to compare objectively measured movement data obtained from Rett patients will facilitate assessment of the patient's performance over time and therapeutic outcomes. It will also increase the potential for Rett-related research centers to share and compare findings thereby increasing the ability to determine if future intervention strategies are effective.

Purpose. The purpose of this report is to describe an objective data acquisition and analysis protocol of gait and posture that will serve to provide an enhanced evaluation of motoric characteristics of individuals with Rett syndrome than is currently conducted.

Method. To establish the feasibility of this protocol, eighteen females ranging in age from 4 to 20 years participated in three basic tasks: overground walking, accelerating treadmill walking, and stationary bipedal postural assessment.

Results. We were able to successfully obtain data from several trials of each assessment task. The feasibility and practicality of obtaining this set of detailed data on gait and posture from individuals with Rett syndrome demonstrates that the protocol can be easily transferred to other gait centers. Even if not all of the assessment technologies are available the collection protocol can easily be adapted.

Conclusion. We suggest that our assessment protocol can provide a standard for objective assessment in a gait laboratory associated with the diagnosis and treatment of Rett syndrome.

KEYWORDS
Rett, gait, posture, kinematics

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INTRODUCTION

Rett syndrome (RTT, OMIM #312750) is a severe neuro-developmental disorder, characterized by apparently normal initial development for about 6-18 months, followed by a period of regression of skills including loss of functional hand use, language and communication and the emergence of characteristic stereotyped hand movements.1 RTT occurs approximately in 1 in every 10,000 births with the condition almost exclusively affecting females and is associated with mutations of the Methyl-CpG-binding protein 2 (MECP2) [1]. When assessed using the International Classification of Functioning, Disability and Health instrument (version 2.1a), the bodily functions that are most often impaired include Sleep (b134), Attention (b140), Memory (b144), Perceptual functions (b156), Higher level cognitive functions (b164), and Language (b167). These impairments affect communication (d3), mobility (d4), and self-care (d5). RTT symptoms include stereotypical hand wringing, breathing abnormalities, abnormalities in muscle tone, loss of social interactions, lack of language skills and overall impaired cognitive functioning [2]. Gait abnormalities feature prominently; they are part of the main criteria for clinical diagnosis of RTT [1]. About 60% – 70% of girls with RTT acquire ambulation [3-6] and their ambulation parallels disease progression [7]. Ambulation is furthermore an independent modifiable risk factor of survival in RTT [8].This range of complex symptoms presents a unique set of challenges associated with the assessment of gait and posture disorders associated with RTT. The inability to effectively communicate using language makes it difficult for the patient to understand the tasks they are being asked to perform. Additionally, the overall deficiencies in movement control also contribute to the difficulty in collecting data using assessment technologies that are traditionally used in movement control assessment centers. Therefore it has become paramount to develop tools to assess progress made through vigorous efforts to improve educational, medical, and psychosocial issues related to Rett syndrome, such as objective gait and mobility assessment presented in this paper. Other assessment tools, such as eye-gaze based assessments of their communication abilities and educational needs are currently being developed in parallel by other groups.

All currently available data on gait in RTT is descriptive in nature, derived on a purely observational basis including, in rare occasions, video assessments by movement disorder specialists [3, 4, 9], and not on quantifiable objective measurements. Gait in RTT has been described in general terms as being dyspraxic, ataxic and influenced by varying degrees of dystonia. It has also been found to be rigid with a tendency for retro-pulsion and contain interspersed freezing episodes [3, 4, 9].

A purely descriptive analysis is intrinsically limited and lacks the potential to clearly discern components that influence overall gait in RTT. As clinical trials designed to test drugs or new therapeutic approaches to RTT are becoming increasingly available, it is important to objectively and accurately measure any potential modification in functioning associated with a given intervention. Without such evaluation, the effectiveness of any potential intervention may be undetected or obscured [10-12]. Both traditional physical therapy interventions, including robot assisted gait training, as well as novel methods such as focused neuromodulation [13] in cortical or cerebellar regions associated with movement control may hold promise for RTT patients but, as mentioned, objective and accurate behavioral measures are necessary to effectively assess the outcomes associated with neuomodulatory interventions. This paper presents a battery of assessments, as performed in a professional gait center, specifically adapted for ambulatory individuals with RTT, which we propose become a standard for gait and postural assessment in RTT.

METHODS

Participants

Eighteen females ranging in age from 4 to 20 served as participants. Sixteen participants had been diagnosed classic RTT, with the remaining two being diagnosed with atypical RTT. All were in the 'stationary' stage as defined by Chahrour and Zoghbi [2] as none of the older girls had entered the 'late motor deterioration' stage and have remained ambulatory. All were receiving evaluation and treatment at the Blue Bird Circle Rett Center at Baylor College of Medicine in Houston, TX. Besides a diagnosis of RTT, inclusion criteria included the ability to independently ambulate, free of walkers, canes or orthotics, possess a level of cognitive functioning that enabled them to understand the assessment tasks after demonstrations by the clinical assistants and parents and remain standing relatively 'quietly' on a posture platform. Quietly in the context of posture testing indicates the patient was able to stand with both feet on the posture platform without assistance. The parent(s) of each participant provided informed consent, including those parents whose daughters were of adult age. All procedures were approved by the Institutional Review Board of the Baylor College of Medicine. The large age range and behavioral characteristics of the participants enabled us to explore a variety of posture and locomotion testing procedures to determine the feasibility of conducting these evaluations with RTT patients. Given the motoric symptoms associated with RTT is was not possible to accurately determine the laterality of our participants.

Movement Tasks

The movement assessment protocol consisted of two walking tasks and one bipedal posture test.

Overground Walking

The overground walking task consisted of four passes over a 4.27 m long x 61 cm wide instrumented walking carpet (GAITRite®) that contained pressure activated sensors. The walkway provided measurements of the spatiotemporal gait parameters. Each trial began with the clinical assistant positioning the participant at the head of the walkway and verbally initiating traversal of the walkway. Depending upon the stride length of each participant, the number of strides collected varied from 4

to 8 per trial. If a participant refused to complete the trial, walked completely off the walkway or turned around and walked back toward the initiation point, that particular trial was discontinued and repeated.

The GaitRite software is designed to automatically identify heel strike and toe off based on pressure distributions and calculate the above measures based upon those events. This automatic processing of the GaitRite data often functioned well. However, based on the participants' walking behavior such as toe-walking, freezing, walking off the walkway, or stepping in place, the software was occasionally unable to automatically identify gait kinematic events. In these cases, the software supported individual stride event identification technics that could be used to ensure the data were accurately representing strides. Although the GaitRite walkway provides a multitude of gait-related variables, variables were selected that facilitated direct comparisons between overground and treadmill walking (see Table 1).

Table 1. Collected spatial and temporal gait variables

Variable
Velocity (m/s)
Stride Length(cm)*
Stance Time (s)*
Swing Time (s)*
Stance Time[% of Gait Cycle]*
Swing Time [% of Gait Cycle]*
Double Support [% of Gait Cycle]*
*Collected bilaterally

Treadmill Walking

The treadmill walking task was completed on a motorized treadmill (Bertec®). The assessment consisted of approximately three minutes of walking with a gradual increase in speed. The participants were fitted with a safety harness suspended from a frame surrounding the treadmill. The task began at a very slow walking speed of 0.2 m/s and was increased by 0.1 m/s approximately every 20 s until the experimenter determined the participant was at the maximal speed for each participant. This maximal speed was determined based upon the participant's walking pattern and exhibited behaviors (focus of attention, hand and facial gestures) as well as suggestions of the parents.

Three dimensional lower limb kinematics were collected using a 12 camera motion capture system (Vicon®) that detected reflected markers that had been placed bilaterally on the toe, heel, ankle, knee, and hip. The kinematic data were collected at 100Hz and a custom script using MATLAB (MathWorks) was developed to filter the three-dimensional marker positions by the application of a Butterworth low-pass filter with the cut-off frequency of 6 Hz.

During treadmill walking, stride time was defined as the period between one heel contact to the next ipsilateral heel contact. The joint angles were calculated from the kinematics data utilizing biomechanical algorithms.14 Some participants walked only on their toes, negating the use of a heel strike to determine the initiation of a stride. In these cases, toe strike was used as the point of a particular stride's initiation, and thus it was possible to determine stride time and associated kinematics. To determine if slight changes in treadmill speed impacted the control of gait, the data from the identified strides were time normalized such that each stride was represented as 100 data points. Each reported kinematic variable (see Table 1) was then reported as a percentage of stride time. A motion capture system using as few as four cameras can be used to obtain reliable sagittal plane kinematic data during treadmill walking.

The following sagittal plane kinematic variables were obtained for each stride from normalized trials (Fig 1). Stride length was calculated from the anterior– posterior distance the ankle marker traveled during the period of a heel contact and consecutive ipsilateral toe off. The angles at which the maximum and minimum peaks occurred for the hip, knee and ankle were recorded as well as the time of their occurrence within each stride. Angular values were used to calculate range of motion for each trial. The relative timing of peak joint motion of hip, knee, and ankle joint pairs was calculated using the latency between the peak angles for each combination pairs.

Several measures were used to determine the degree of joint motion symmetry between the two lower limbs. Ratios of left/right leg stride length and percent stance time were calculated for each stride to assess symmetry of gait characteristics. To gain an accurate assessment of the degree of variability the coefficient of variability was calculated for joint motion waveform, each participant and each treadmill speed.

Bipedal Posture Assessment

The SMART Balance Master (Neurocom®) equipped with two force plates was used to complete this assessment. Sensory Organization Test 1 (quiet stance, eyes open) was the only condition tested. This assessment consisted of initially securing the

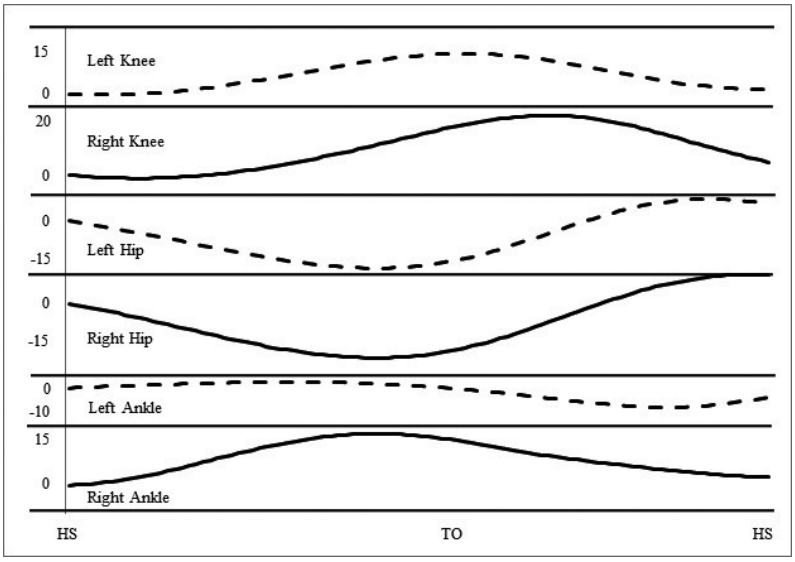

Figure 1. Exemplar time normalized stride (100%). HS – heel strike, TO – toe off. Values on the abscissa reflect joint angles. Positive values represent limb flexion while extension is represented by negative values.

participant in a harness attached to the frame of the Balance Master, followed by positioning her on the two foot plates. Testing began as soon as the participant's feet were on the two foot plates and continued until she lifted either foot off of a plate. This procedure was completed up to five times to obtain at least one 8 second period of 'quiet' stance.

To evaluate postural performance, an Equilibrium Score (ES) was calculated from each 8 second or longer period of quiet stance using the obtained force plate data. The ES uses the maximum anterior-posterior center-of-gravity (COG) displacement data and a theoretical maximum excursion value of 12.5 degrees. The following formula was used to calculate the ES.

$$ES = \frac{12.5 - [\theta \max - \theta \min]}{12.5} * 100$$

The ES ranges from 0-100 with 100 representing no movement of the COG during the trial to 0 representing a 'fall' (i.e. discontinuation of data collection). Given the data was collected at 100 Hz, the criteria that at least 800 consecutive samples of quiet stance, we believe our minimum criterion of 8 seconds provides a large enough sample to apply the formula used to calculate the ES and provide a reliable measure of postural control in a RTT patient population.

The COG data was disaggregated into its anterior posterior (AP) and medio-lateral (ML) time series components. A sway path length in the AP and ML direction (APPlength and MLPlength) were calculated by summing the absolute value of the total displacement of the COG sway. The path lengths were then time normalized by dividing the calculated path lengths by the number of samples obtained for each trial that met the 8 second quiet stance criteria (Fig 2). The minimum of 8 seconds of quiet provided an acceptable time period to effectively calculate the participant's ES and provided enough data to evaluate the medio-lateral and anterior-posterior components of postural control.

Although we anticipated that the lower limb kinematic patterns would approximate the patterns observed during healthy gait we expected that the variability of those patterns would be substantially increased. Furthermore, we expected the participants to maintain their COG within their base of support during the postural control testing but we again anticipated increased variability relative to healthy patterns of COG motion. It is important to note that our collection and analysis methodology enabled us to accurately characterize the participants performance during gait and posture testing such that the resulting data can confidently be used for comparisons with data collected following pharmacological or therapeutic interventions in the RTT population.

Collection Challenges

When collecting movement-related data using a variety of technologies with participants who have both physical and cognitive challenges, it is important to accept that the standardization of procedures traditionally followed with healthy individuals may require some modifications. Although individuals with RTT present a variety of similar behaviors, each displays a unique set of characteristics which can present challenges during data collection and necessitate intervention. From our experiences, these challenges and interventions fall into three major categories: first verbal and visual encouragement by family members and clinical assistants was used to motivate the participant to complete a given task and second, light touch by the clinical assistants to guide the participant during the task. For example, light touch on the elbow or shoulder to encourage the participant to continue to traverse the overground walkway, continue walking on the treadmill or standing still during posture

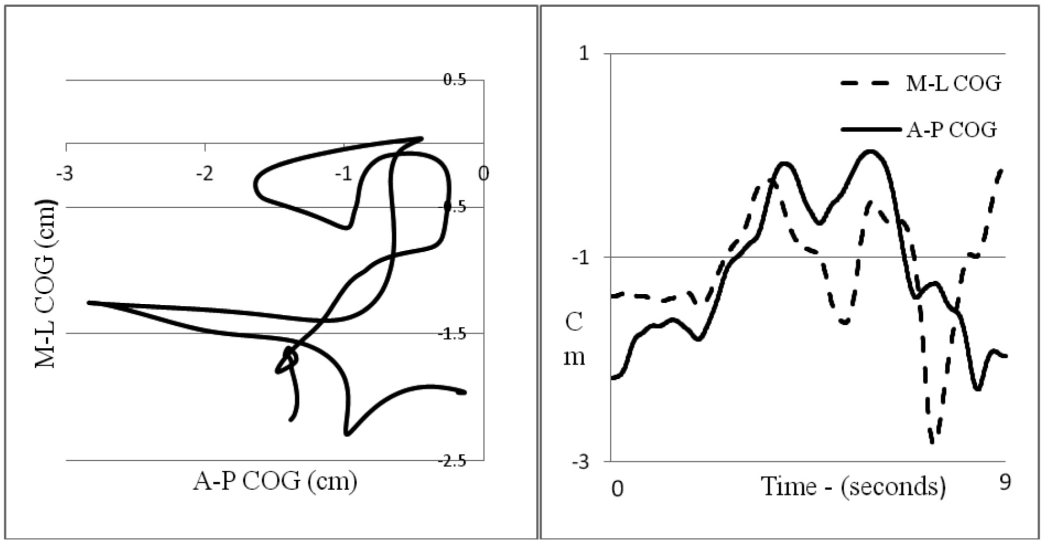

Figure 2. Exemplar Center of Gravity (COG) record. A: Medio-lateral (M-L) versus anterior-posterior (A-P) COG data. B: M-L and A-P COG time series data. Time normalized M-L path length – 0.0104, time normalized A-P path length = 0.0076. Equilibrium score = 81. The same data is represented in both A and B.

testing. These first two categories of 'assistance' are not used when collecting movement-related data, but were critical protocol modifications for our participants that enabled us to obtain useful and reliable data.

The third major category of challenges involved the walking behaviors exhibited by the participants. Participants occasionally quit walking in the middle of a trial whether on the GaitRite or treadmill. If they stopped walking while on the treadmill, the treadmill belts would carry them to the back of the treadmill for as long as there was slack in the harness attachments. Once the slack was taken up, the participants experienced a slight 'jerk' and that would always trigger the participant to begin walking again. If they stopped walking during the overground assessment, it was at that point that encouragement was escalated. A related challenge resulting from disordered movement patterns was the loss of the reflective markers during treadmill walking. Occasionally the data collected needed to be paused to reapply the reflective markers.

These tasks can be completed in any order as the performance of one should not impact the performance on another task. However, we recommend performing the overground gait and posture assessments prior to the treadmill walking task. The reason being that the first two assessments do not require any preparation. The participant either steps onto the gait assessment mat or the posture platform and performs the task. Conversely, the treadmill walking assessment requires that the reflective markers be placed over a number of sites on the body that may serve to agitate to patient, thereby increase the difficulty in gaining the participant's cooperation that is needed for additional testing.

LIMITATIONS

The primary limitation associated with our suggested protocol is that it requires RTT participants to be independently ambulatory. Given that many RTT patients become wheelchair bound during their teenage years, our protocol cannot be used to assess a substantial percentage of RTT patients which, by its nature, limits the protocol's ability to provide a comprehensive assessment of RTT motoric capabilities. Another limitation is for the protocol to be effectively implemented requires some relatively expensive assessment technologies and clinical investigators that many basic clinics are unlikely to possess. However, we anticipate that most of the larger pediatric care centers and specialized RTT centers across the world either have the technology we used or functional variants of it or have access to it through existing collaborations, thus facilitating implementation of our proposed protocol.

Although we did not assess our participants across multiple days, the number of strides (for overground and treadmill walking) and the number of data samples obtained from the posture testing provide reliable measures that can be used to characterize an individual patients' performance at a given point in time. Therefore, we are confident our measures can be used to accurately determine both baseline performance and any systematic changes resulting from either a pharmacological or therapeutic intervention.

CONCLUSION

With a view towards the emergence of clinical trials and exploratory behavioral interventions [10, 12, 15, 16] in rare disorders such as RTT, it becomes extremely important to develop objective measurement protocols that are designed to evaluate the effectiveness of these interventions [10-12]. As a majority of these clinical trials will be performed on a multi-center basis, it will be vital that these protocols be objective and repeatable, in order for results to be readily cross-validated across laboratories and

clinics. The proposed protocol also promotes the objective measurement of performance changes over time within an individual patient. Such information has been used in other patient populations and can be instrumental in guiding clinical intervention decision making. It is important to obtain measures of both static and dynamic bipedal behavior in order to assess how these two categories influence each other and to adequately identify the underlying mechanisms leading to abnormal gait and bipedal postural in RTT. There are literally hundreds of variables that can be utilized to characterize gait and posture control. The variables included in the current protocol represent a compromise between an exhaustive, time consuming, expensive analysis and one that would include too few variables to adequately detect potentially subtle changes in behavior (i.e. outcomes) after interventions in this patient group.

DISCLOSURES

The authors report no competing interests. C.S. Layne was responsible to conceptualization of the project, data collection and analyses and the development of the manuscript. B-C Lee was responsible to conceptualization of the project, data analyses and the development of the manuscript. D. Young was responsible for data collection and analyses and manuscript review. D. G. Glaze served as senior mentor and contributed to conceptualization of the project and manuscript review. B. Suter was responsible to conceptualization of the project, data collection and analyses and the development of the manuscript.

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Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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