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Pathological Gait in Rett Syndrome: Quantitative Evaluation Using Three-Dimensional Gait Analysis

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Abstract:	Objectives: Ataxic-rigid gait is a characteristic gait pathology in patients with Rett syndrome (RTT). In the present study, we aimed to quantitatively evaluate gait pathology in patients with RTT using three-dimensional gait analysis (3DGA). Methods: We performed 3DGA in 11 patients with RTT ranging from 5 to 18 years (median age, 9 years) and in 33 age-matched healthy female controls. We compared the results of 3DGA, including spatiotemporal gait parameters and comprehensive indices of gait kinematics, such as the Gait Deviation Index (GDI) and Gait Profile Score (GPS), between the two groups. The GPS consists of nine sub-indices called Gait Variable Scores (GVSs). Decline in GDI or elevation of GPS and GVS indicated greater abnormal gait pathology. Results: The patients demonstrated significantly slower walking speed, lower step length/length of the lower extremities, lower cadence, wider step width, and higher coefficient of variation of step length than the controls. Moreover, the patients had a lower GDI and higher GPS than the controls. The patients also exhibited higher GVSs for eight out of nine gait kinematics, particularly the sagittal plane in the pelvis, hip, knee, and ankle joint; coronal plane in the pelvis and hip joint; and horizontal plane in the pelvis than the controls. Conclusions: Quantitative evaluation of gait pathology in patients with RTT is possible using 3DGA. We found that in addition to ataxic-rigid gait, abnormalities in the coronal plane of the pelvis and hip joint and the horizontal plane of the pelvis were prominent.
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Response to Reviewers:	Reviewer #1 - Page 7, line 51 "We checked distribution of ataxia, muscle tone abnormality, rigidity, and dystonia" Since rigidity is a muscle tone abnormality the authors should remove rigidity from the sentence, or refer to all muscle tone abnormalities (hypotonia, spasticity, rigidity). Response: Thank you for the valuable suggestion. We agree with your opinion. Accordingly, we have removed the term “rigidity” from the sentence as follows (page 7, lines 12-14): “In the physical examination, muscle tone, ataxia, dystonia, scoliosis, pes planovalgus, and range of motion for each joint were evaluated. We checked the distribution of muscle tone abnormality, ataxia, and dystonia.” - Page 11 Line 29 "Ataxia and rigidity were seen in the entire body of all six and five patients presenting these findings, respectively" In neurology, "generalized" would be a better term to address involvement of the entire body. This comment includes also Table 1. Ataxia is usually defined by axial, appendicular or gait involvement (truncal ataxia, limb ataxia, gait ataxia). I would address this motor disorder in this way rather than involving or not the entire body. This comment includes also Table 1. Response: Thank you for your insightful suggestion. We apologize for not using the terminology appropriately. Accordingly, we have changed the descriptions of the neurological findings in the Results section (page 11, lines 7-10) and Table 1: “Physical examination revealed that muscle tone was hypotonia in three patients, hypertonia in four patients, and rigidity in five patients. All abnormalities of muscle tone were generalized. Ataxia was seen in six patients and all of them showed appendicular, axial, and gait involvement.”

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Highlights

- We performed three-dimensional gait analysis on patients with Rett syndrome.
- Patients showed decreased walking speed, step length, and cadence than controls.
- Patients demonstrated increased step width and gait variability than controls.
- Patients showed reduced gait quality related to ataxic-rigid gait in sagittal plane.
- Prominent abnormalities in the coronal and the horizontal planes were also observed.

Abstract

Objectives: Ataxic-rigid gait is a characteristic gait pathology in patients with Rett syndrome (RTT). In the present study, we aimed to quantitatively evaluate gait pathology in patients with RTT using three-dimensional gait analysis (3DGA).

Methods: We performed 3DGA in 11 patients with RTT ranging from 5 to 18 years (median age, 9 years) and in 33 age-matched healthy female controls. We compared the results of 3DGA, including spatiotemporal gait parameters and comprehensive indices of gait kinematics, such as the Gait Deviation Index (GDI) and Gait Profile Score (GPS), between the two groups. The GPS consists of nine sub-indices called Gait Variable Scores (GVSs). Decline in GDI or elevation of GPS and GVS indicated greater abnormal gait pathology.

Results: The patients demonstrated significantly slower walking speed, lower step length/length of the lower extremities, lower cadence, wider step width, and higher coefficient of variation of step length than the controls. Moreover, the patients had a lower GDI and higher GPS than the controls. The patients also exhibited higher GVSs for eight out of nine gait kinematics, particularly the sagittal plane in the pelvis, hip, knee, and ankle joint; coronal plane in the pelvis and hip joint; and horizontal plane in the pelvis than the controls.

Conclusions: Quantitative evaluation of gait pathology in patients with RTT is possible using 3DGA. We found that in addition to ataxic-rigid gait, abnormalities in the coronal plane of the pelvis and hip joint and the horizontal plane of the pelvis were prominent.

Key words: Rett syndrome; three-dimensional gait analysis; ataxic-rigid gait; dystonia

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Pathological Gait in Rett Syndrome: Quantitative Evaluation Using Three-dimensional Gait Analysis

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List of abbreviations:

3DGA, three-dimensional gait analysis; GDI, Gait Deviation Index; GPS, Gait Profile Score; GVS, Gait Variable Score; *MECP2*, methyl-CpG-binding protein 2; MRI, magnetic resonance imaging; RTT, Rett syndrome

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1. INTRODUCTION

Rett syndrome (RTT) is a neurological disorder with an estimated prevalence of 1 per 10,000 girls [1-4]. Pathogenic mutations in the methyl-CpG-binding protein 2 (*MECP2*) gene have been confirmed in more than 90% of the classic cases [5]. While patients with RTT demonstrate normal early development, they subsequently show developmental regression and exhibit various neurological symptoms, such as acquired microcephaly, epilepsy, and movement disorders, represented by stereotypical hand movements and gait disturbance [1,2]. Underlying mechanism causing these movement disorders in RTT has been discussed over time.

Gait problems are common in patients with RTT. Approximately half of the patients aged ≥10 years cannot walk independently [6], and ambulatory patients exhibit a slow walking speed and short step length once the disease is established [7,8]. Ataxic-rigid gait is the most common and characteristic gait in patients with RTT [5,7-9]. It is characterized by a wide-base, unsteady gait with abnormal muscle contraction, and hyperextension of the lower extremities [8]. Past studies on gait pathology in patients with RTT mainly depended on visual observation with or without video records [7-9]. Therefore, the results of gait evaluation were highly dependent on the abilities of the evaluators.

The three-dimensional gait analysis (3DGA) system is a reliable modality for

quantitatively evaluating gait using spatiotemporal gait data, gait kinematics, and gait kinetics [10]. Comprehensive indices based on kinematics of the lower extremities and pelvis, such as the Gait Deviation Index (GDI) and Gait Profile Score (GPS), emerged in the 2000s [11,12]. These indices can help specialists appropriately evaluate overall gait pathology. In addition, digitalization of gait deviation using these indices is beneficial, especially for non-specialists, including parents of the patients and general pediatricians, to understand the severity of pathological gait. Specific gait characteristics of pediatric neurological diseases have been reported using 3DGA and other indices [13,14].

To date, quantitative information regarding gait evaluation in patients with RTT using 3DGA is limited. The main focus of some of the existing studies was on the changes associated with treadmill walking, while data from comparisons with healthy controls are lacking [15,16]. In the present study, we performed 3DGA in patients with RTT and in healthy women. The aims of this study were as follows: 1) to evaluate pathological gait, including ataxic-rigid gait, objectively and quantitatively in patients with RTT and 2) to detect new gait characteristics, which are difficult to detect without 3DGA, in patients with RTT.

2. MATERIALS AND METHODS

2.1. Ethical standards

This study was approved by the research ethics boards of Nagoya University (approval number 2021-0230) and Aichi Prefecture Mikawa Aoitori Medical and Rehabilitation Center for Developmental Disabilities (approval number RH30001). Written informed consent to participate and for publication was obtained from the parents of all the participants prior to their inclusion in the study. This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.2. Study population

We enrolled patients with RTT who were referred to our hospital between October 2020 and August 2021 for motor function evaluation. All the patients were examined by a pediatric neurologist and pediatric orthopedic surgeon for eligibility. The inclusion criteria were as follows: 1) clinical diagnosis of RTT, 2) genetic confirmation of *MECP*2 mutations, and 3) ability to walk independently according to instructions. Patients with severe visual and hearing disabilities that could affect gait pathology were excluded.

During the study period, 11 patients with RTT were referred to our hospital, and all

were included in the present study. The target number of the control group was set to three times that of the patient group as recommended in the previous report; therefore, 33 healthy girls from the Okazaki child medical checkup enrolled for physical function study group were included in the control group [17,18].

2.3 Clinical data of patients with Rett syndrome

We studied the demographic, clinical, and genetic data from interviews with parents and reviews of medical charts. Demographic and clinical data included age, sex, height, weight, length of the lower extremities, age at which the participant started walking independently, ability to speak, frequency of epileptic seizures, and antiseizure medication. The results of brain magnetic resonance imaging (MRI) and genetic testing for the *MECP2* gene were assessed. In the physical examination, muscle tone, ataxia, dystonia, scoliosis, pes planovalgus, and range of motion for each joint were evaluated. We checked the distribution of muscle tone abnormality, ataxia, and dystonia. We also evaluated severity of dystonia using the Burke-Fahn-Marsden Dystonia Rating Scale [19]. This scale consists of two subscales: dystonia movement scale (maximum = 120 points) and disability scale (maximum = 30 points); higher points indicate more severe dystonia. If the patient had scoliosis, severity was classified into three groups: mild (10˚ ≤ Cobb

angle < 25˚), moderate (25˚ ≤ Cobb angle < 40˚), and severe (40˚ ≤ Cobb angle) [20].

2.4 Three-dimensional gait analysis

We used an instrumented 3DGA system (MX-T 20S; Vicon Motion Systems Ltd., Oxford, UK), which included eight optical cameras and eight force plates (Advanced Mechanical Technology, Inc., Watertown, MA, USA), to measure spatiotemporal gait variables. In our institution, during 3DGA, a trial means that the participant walks barefoot 2 m of measuring flat tract embedded with eight force plates, which is focused by eight optic cameras. There is 3 m of adjunctive tract before and after measuring flat tract (Supplementary Figure 1). The sampling frequency was set to 100 Hz. An experienced pediatric physiotherapist attached 24 retro-reflective markers to the subjects according to the Conventional Gait Model 2.3 [21]. The gait of the participants was recorded at a self-selected speed. The mean result of total six steps (three trials; one trial included one step for left and right) for every patient was used for the data analysis. In the present study, mean values for each participant were first computed, and then grand mean values for patients and control groups were calculated.

2.5 Data analysis

We recorded, preprocessed, and analyzed the gait variable data using the Vicon Nexus 2.11 (Vicon Motion Systems Ltd., Oxford, UK) and assessed walking speed, step length, cadence, step width, gait variability, GDI, GPS, and Gait Variable Scores (GVSs). Step length was normalized using length of the lower extremities to exclude the effect of physique, and step length/length of the lower extremities was used for comparing patients with Rett syndrome and healthy controls.

Gait variability was calculated using the coefficient of variation (standard deviation/mean value × 100) of step length [22]. The GDI was calculated based on nine clinically important kinematic factors (pelvis and hip in the sagittal, coronal, and horizontal planes; knee and ankle in the sagittal plane; and foot progression angle) [11]. A total of 459 kinematic data points (9 angles × 51 points [every 2% of the gait cycle]) throughout the entire gait cycle was captured and used for analysis. GDI was established to fulfill following conditions: 1) 100 points present mean of healthy adults and 2) for every 10-point decline from that mean, one standard deviation was reduced from the normal value [11]. The GVSs were calculated based on the root mean square differences between particular kinematic data points of the participants and mean data of the reference population across the gait cycle [23,24]. The GPS was composed of nine clinically important GVSs: pelvic tilt, pelvic obliquity, pelvic rotation, hip flexion, hip abduction,

hip internal rotation, knee flexion, dorsiflexion of the ankle, and foot progression angle, the last six for which, the scores of the left and right lower extremities were included separately. Therefore, a total of 15 kinematic data points were used for the calculation of GPS [25]. Elevated GPS and GVS indicated abnormal gait pathology. The minimal clinically important difference in the GPS was reported to be 1.6° [25]. Median and interquartile range of the GPS for healthy controls in a previous report were 5.2° and 1.9°, respectively [23].

2.6 Statistical analysis

To compare continuous variables, the Shapiro–Wilk test was used to determine whether the variables were normally distributed. Subsequently, the two-sample t-test was used to compare normally distributed variables after assessing variance using the Levene's test. The Mann–Whitney U test was used to compare variables with a non-normal distribution. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM, Armonk, NY, USA). A P value <0.05 was considered statistically significant.

3. RESULTS

The clinical characteristics of the 11 patients who underwent RTT are shown in Table 1. The median age of the patients was 9 years (range: 5–18 years). Epileptic seizures were observed in nine patients, all of who were taking at least one antiseizure medication. Regarding mutations in the *MECP2* gene, two patients exhibited exon deletion; two, a nonsense mutation; and the others, a missense mutation. Brain MRI showed mild atrophy in three cases; however, specific lesions in the basal ganglia or cerebellum were not detected. Physical examination revealed that muscle tone was hypotonia in three patients, hypertonia in four patients, and rigidity in five patients. All abnormalities of muscle tone were generalized. Ataxia was seen in six patients and all of them showed appendicular, axial, and gait involvement. Dystonia in the resting state was seen in four extremities of one patient, and dystonia movement scale and disability scale were four and one, respectively. Scoliosis, pes planovalgus, and restriction of ankle dorsiflexion were exhibited in six, five, and ten patients, respectively. Severity of scoliosis was mild in five patients and moderate in one patient.

The spatiotemporal gait parameters in patients and age-matched healthy controls are shown in Table 2. Patients with RTT showed a significantly slower walking speed, decreased step length/length of the lower extremities, lower cadence, and wider step than the controls. The coefficients of variation of step length were significantly higher

in patients with RTT. The comprehensive indices of gait kinematics in patients and controls are shown in Table 3. The patient group exhibited a lower GDI and a higher GPS than the control group. The GVSs for eight out of nine kinematic factors were significantly higher in the patient group than in the control group. Figure 1 shows a comparison of the median and interquartile range of GVSs between patients with RTT and healthy controls. Greater differences were seen in the following gait kinematics: sagittal plane in the pelvis, hip, knee, and ankle joint; coronal plane in the pelvis and hip joint; and horizontal plane in the pelvis. Figure 2 exhibits mean waveforms of nine major kinematics, which were included in GDI, GPS, and GVS for both groups, patients with RTT and healthy controls. Patients with RTT exhibited insufficient extension of the hip joint in terminal stance, decreased dynamic range of motion in the knee joint, excessive plantarflexion in the ankle joint, excessive external rotation in the foot progression angle, and excessive rotation in the pelvis in addition to a larger variation in many kinematics than the healthy controls.

4. DISCUSSION

To the best of our knowledge, this is the first study in which a comparative 3DGA was performed between patients with RTT and healthy controls. Patients with RTT

demonstrated a significantly slower walking speed, smaller step length/length of the lower extremities, lower cadence, wider step, higher coefficients of variation of step length, higher GPS, and lower GDI than the healthy controls. Furthermore, these patients had higher GVSs for eight out of nine major gait kinematics. Our results may help clinicians select suitable interventions for pathological gait in patients with RTT, such as programs with a focus on coronal and horizontal abnormalities to improve gait abilities.

Ataxic-rigid gait, which is a wide-base, unsteady gait, is a characteristic gait pathology in patients with RTT [9]. The higher coefficients of variation of step length demonstrated in this study may be indicative of ataxic gait [22,26]. We also observed a greater step width in the patient group, which may be synonymous with wide-base gait that indicates gait instability. Higher GVSs in the sagittal plane of the hip, knee, and ankle joints were consistent with the features of rigid gait. Comparison of mean waveforms revealed that patients with RTT had a narrower dynamic range of motion in the knee joint and this finding was also consistent with rigid gait. Considering these variables in combination, ataxic-rigid gait was objectively evaluated in patients with RTT.

In addition to gait abnormalities indicating ataxic-rigid gait, we detected certain gait characteristics in the patients with RTT. First, the patients had higher GVSs related to the coronal plane of the pelvis and hip joint than the controls. Scoliosis, which is a

common comorbidity of RTT, is one possible reason for the deviation of kinematics in the coronal plane from normal gait [7,8,27]. Another presumable reason is that a greater abduction of the hip joint was needed to make a wide base for stabilizing gait. Second, the GVS in the horizontal plane of the pelvis was higher in the patients than that in the healthy controls. The asymmetric abnormalities in the horizontal plane may be attributed to dystonia because these abnormal horizontal rotations were not observed when the patients were in the resting state [7,8,27]. We attempted to analyze the association between the findings (severity of scoliosis, distribution, and severity of dystonia) and gait variables, however, this was difficult because severity of scoliosis was mild in all patients except one, and dystonia was seen only in one patient. Comparison of mean waveforms exhibited a larger rotation of the pelvis in patients with RTT. This could be partly explained by swinging the lower extremities larger for compensation of a shorter step length.

The basal ganglia may be involved in gait rigidity and dystonia exhibited by patients with RTT. In a recent study using susceptibility-weighted imaging in patients with Rett aged between 4 and 28 years, Jan et al. reported that increased dystonia and increased iron accumulation in the dopaminergic system, including the basal ganglia, were observed with age, and dystonia was positively correlated with iron accumulation

[28]. This hypothesis for the underlying mechanism of rigidity/dystonia could explain the fact that dystonic-type rigidity becomes established as the child gets older [27, 29-31]. Additionally, involvement of the cortico-basal ganglia-thalamo-cortical loop has been suggested [27].

The underlying mechanism of ataxic gait in patients with RTT has also been elucidated. Functional deterioration of the subcortical, cerebellar, and spinal cord networks that causes ataxia and gait abnormalities as the disease progresses has been indicated in a previous electroencephalography study [32]. Recently, a voxel-based volumetric brain MRI study showed decreased cerebellar volumes in children with RTT compared with those in the controls [33]. There were no statistically significant differences in cerebral volumes between the two groups, and it was concluded that decreased cerebellar volumes might be an early brain abnormality associated with RTT [33]. These functional and structural abnormalities of the central nervous system may cause ataxic gait even in childhood.

Our findings showed a slower walking speed, shorter step length, lower GDI, and higher GPS in patients with RTT than in the controls. While a slower walking speed and shorter step length were consistent with the findings of previous studies, including those reported by Dr. Andreas Rett [8,9], these features are also associated with other

neurological diseases characterized by unsteady gait pattern [34-36]. The lower GDI and higher GPS observed in patients with RTT were expected considering their highly deviated gait pattern; furthermore, these values are linked to various neurological or orthopedic gait pathologies. Out of our study results, a lower GDI and higher GPS may aid in focusing on evaluating disease severity and changes over time.

Thus, using 3DGA, the objective and quantitative evaluation of gait pathologies is potentially possible in clinical practice. Abnormalities in the horizontal plane were difficult to detect by visual examination. Evaluating gait pathology while concentrating on subtle but important differences can lead to more suitable and tailored rehabilitation. Another benefit of quantitative gait evaluation is the effectiveness of treatment. Currently, many treatment approaches, including brain-derived neurotrophic factor augmentation, insulin-like growth factor-1 augmentation, and gene replacement, are being developed [2]. The requirement for biomarkers that can help evaluate the effectiveness of these treatments is increasing [36]. GDI, GPS, and GVS may be useful indices for ambulatory patients because they reflect abnormalities in gait, which is one of the most fundamental and important movements in humans.

This study had some limitations. First, the number of patients was too low; therefore, the statistical analysis was inadequate. Thus, factors, such as the correlation between

MECP2 genotype and gait pathology, remain unclear. However, most spatiotemporal gait parameters and gait kinematics were significantly different between the patients and controls, despite this small number. Second, while comprehensive indices, such as GDI, GPS, and GVS, can help evaluate overall gait pathology, they alone cannot be used to describe detailed gait patterns. Therefore, hyperflexion or hyperextension of the knee joints could not be explained by high GVS in the sagittal plane of the knee joint. Third, the age of the patients ranged widely. Nevertheless, we have described the general gait characteristics regardless of their changes with age. Fourth, we only performed qualitative assessment of muscle tone abnormality and ataxia. This made it difficult to evaluate how these motor features influence gait variables. Despite these limitations, our study provides objective and quantitative information regarding gait pathology in patients with RTT. Further studies with a large number of patients will be needed to describe more detailed characteristics of pathological gait in patients with RTT.

5. CONCLUSIONS

We performed 3DGA in patients with RTT and compared the results with those of age-matched healthy controls. Patients with RTT exhibited various gait pathologies in both spatiotemporal parameters and gait kinematics. In addition to ataxic-rigid gait,

which has been reported with emphasis on the wide base and hyperextension of the lower extremities, abnormalities in the coronal plane of the pelvis and axial plane of the pelvis were prominent. Objective and quantitative gait evaluation may benefit clinicians by helping them decide on personalized treatment plans for their patients.

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AUTHOR CONTRIBUTIONS

Takeshi Suzuki designed and conceptualized the study, recruited the patients, performed neurological physical examination and statistical analysis, interpreted the data, and drafted the manuscript.

Yuji Ito designed and conceptualized the study, recruited the patients, interpreted the data, and revised the manuscript.

Tadashi Ito performed three-dimensional gait analysis, analyzed and interpreted the data, and revised the manuscript.

Hiroyuki Kidokoro and Tomohiko Nakata designed the study and revised the manuscript.

Koji Noritake performed orthopedic physical examination, interpreted the data, and revised the manuscript.

Keita Tsujimura, Shinji Saitoh, Hiroyuki Yamamoto, Nobuhiko Ochi, Naoko Ishihara, and Izumi Yasui recruited the patients and revised the manuscript.

Hideshi Sugiura provided data of the healthy controls and revised the manuscript

Jun Natsume designed and conceptualized the study, recruited the patients, and revised the manuscript.

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DECLARATION OF INTEREST

Jun Natsume belongs to the Department of the Developmental Disability Medicine in Nagoya University Graduate School of Medicine, which is the laboratory endowed by Aichi Prefecture. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure Captions

Figure 1. Box-and-whisker plot of Gait Variable Scores in patient and control groups

Lower and upper edges of each box exhibit 25 and 75 percentile values of Gait Variable Scores (GVSs), respectively. Vertical lines represent range of GVS. Horizontal lines in boxes and cross marks indicate median and mean values of GVSs, respectively.

Figure 2. Mean waveforms of nine major kinematics

A. Mean waveforms of patients with Rett syndrome. B. Mean waveforms of healthy controls. Unit of vertical scale is degree. Red and green lines show mean of right and left foot in both the groups, respectively. Blue lines show ±1 standard deviation from mean values. With reference to vertical line near the center, left side mean stance phase, and right-side mean swing phase. Patients with RTT exhibited insufficient extension of the hip joint in terminal stance, decreased dynamic range of motion in the knee joint, excessive plantarflexion in the ankle joint, excessive external rotation in the foot progression angle, and excessive rotation in the pelvis in addition to a larger variation in many kinematics than the healthy controls.

Ant/Post: anterior/posterior, Flex/Ext: flexion/extension, Plan/Dors: plantarflexion/dorsiflexion, Int/Ext: internal rotation/external rotation, Add/Abd:

adduction/abduction

Figure_1

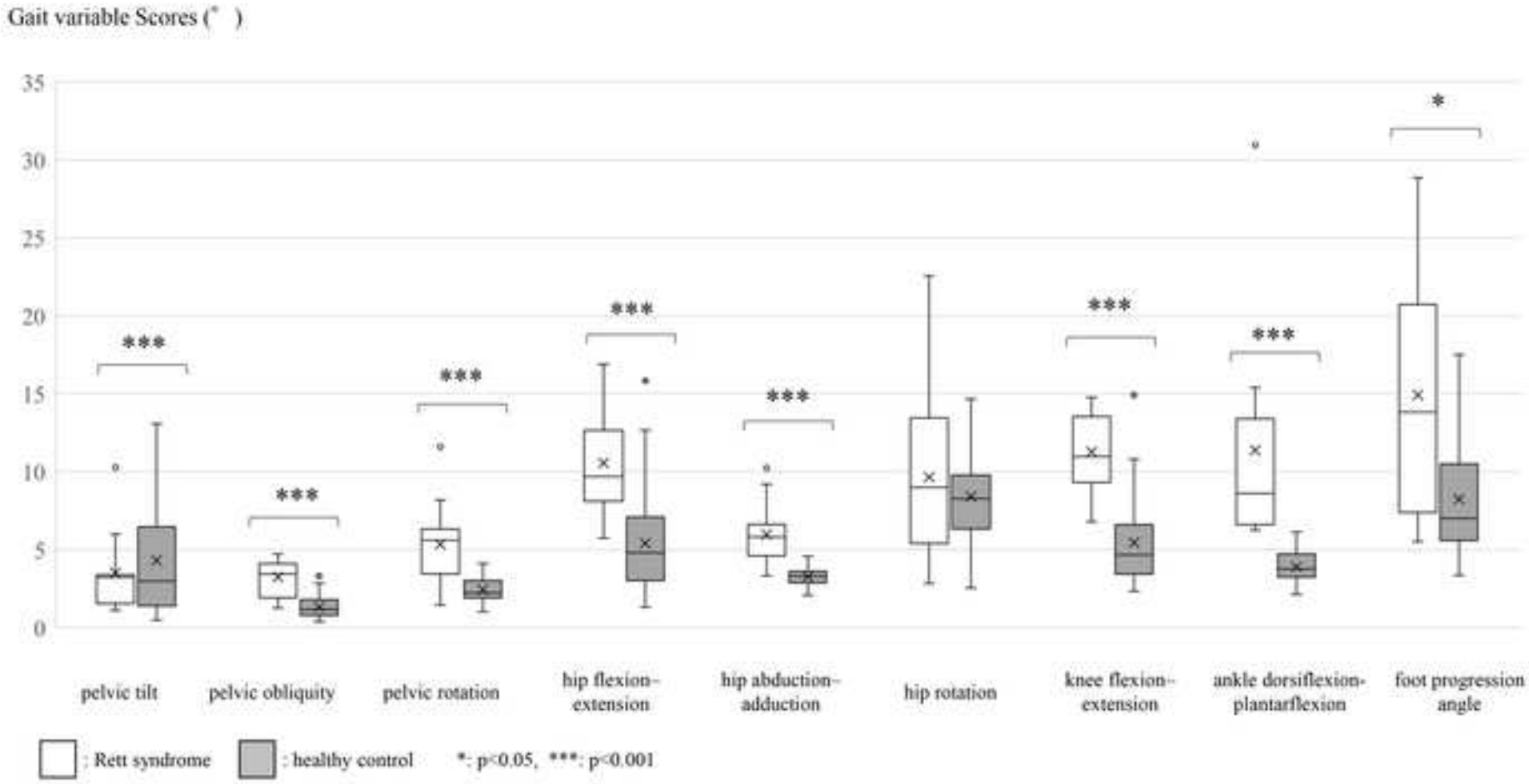
Gait variable Scores (°)
35
30
25
20
15
10
5
0
***
***
***
***
***
***
*
pelvic tilt
pelvic obliquity
pelvic rotation
hip flexion-extension
hip abduction-adduction
hip rotation
knee flexion-extension
ankle dorsiflexion-plantarflexion
foot progression angle
: Rett syndrome
: healthy control
*: p<0.05, ***: p<0.001

Figure 2

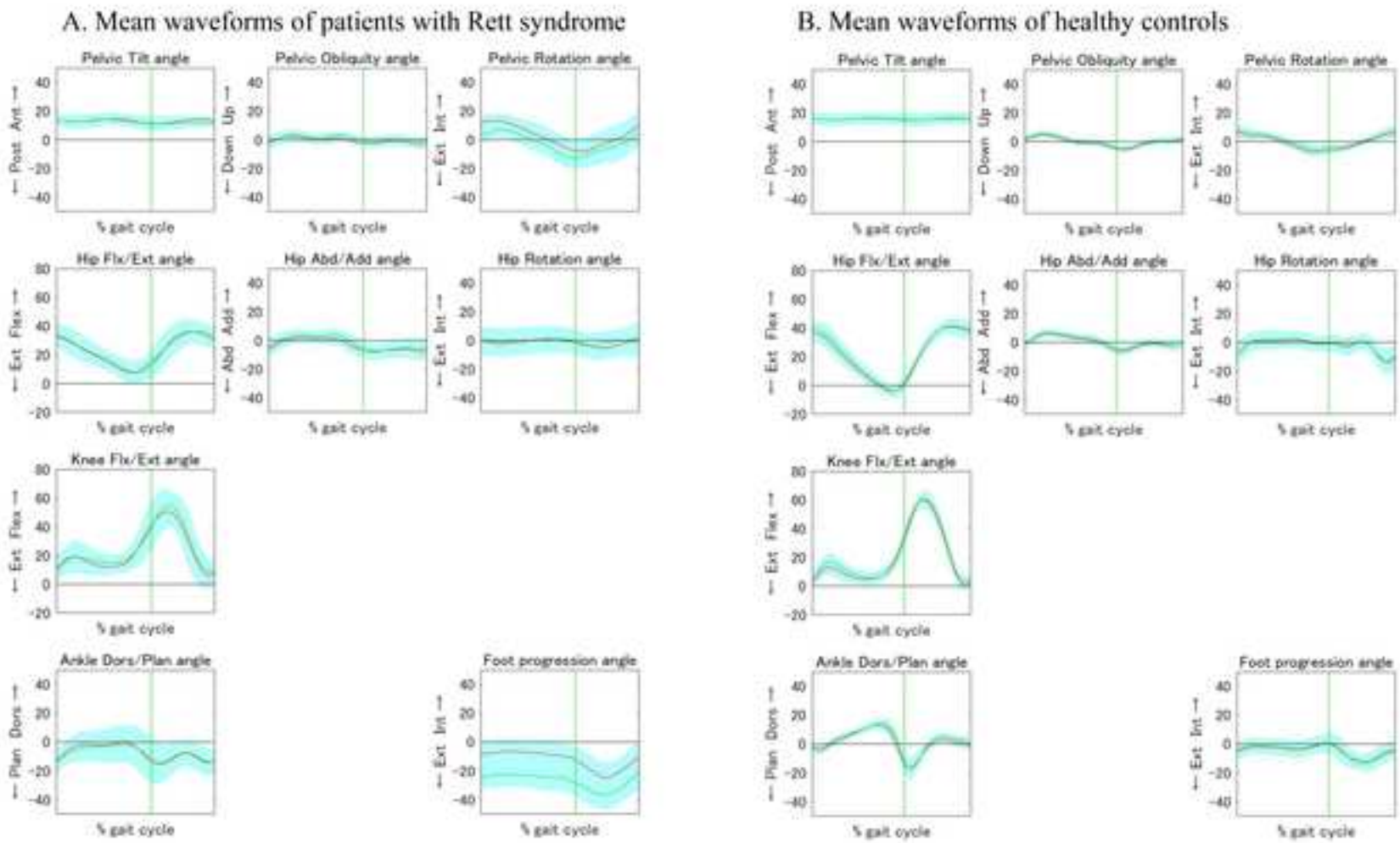
A. Mean waveforms of patients with Rett syndrome
Pelvic Tilt angle
← Post Ant →
Pelvic Obliquity angle
← Down Up →
Pelvic Rotation angle
← Ext Int →
Hip Flx/Ext angle
← Ext Flex →
Hip Abd/Add angle
← Abd Add →
Hip Rotation angle
← Ext Int →
Knee Flx/Ext angle
← Ext Flex →
Ankle Dors/Plan angle
← Plan Dors →
Foot progression angle
← Ext Int →
% gait cycle
B. Mean waveforms of healthy controls
Pelvic Tilt angle
← Post Ant →
Pelvic Obliquity angle
← Down Up →
Pelvic Rotation angle
← Ext Int →
Hip Flx/Ext angle
← Ext Flex →
Hip Abd/Add angle
← Abd Add →
Hip Rotation angle
← Ext Int →
Knee Flx/Ext angle
← Ext Flex →
Ankle Dors/Plan angle
← Plan Dors →
Foot progression angle
← Ext Int →
% gait cycle

Table 1. Clinical characteristics of patients with Rett syndrome at the time of gait analysis

Patient	1	2	3	4	5	6	7	8	9	10	11
MECP2 gene mutation	Missense Arg133Cys	Deletion of exon 3-4	Nonsense Arg270Ter	Missense Thr158Met	Missense Arg306Cys	Nonsense Arg294Ter	Missense Arg133Cys	Deletion of exon 3-4	Missense Arg306Cys	Missense Pro152Arg	Missense Arg133Cys
Age	5 y	6 y	7 y	7 y	8 y	9 y	9 y	13 y	15 y	18 y	18 y
Age at which independent walking started	1 y 2 mo	1 y 4 mo	1 y 10 mo	2 y 0 mo	1 y 3 mo	2 y 0 mo	1 y 3 mo	1 y 2 mo	1 y 6 mo	1 y 2 mo	1 y 8 mo
Frequency of epileptic seizures	Yearly	Weekly	Yearly	Monthly	None	Yearly	None	Yearly	Yearly	Monthly	Monthly
Antiseizure medication	VPA	LEV	VPA, LEV	VPA, LEV, LCM	None	LEV	None	ZNS	VPA, LEV, PB	CBZ	VPA, LTG
Speech ability	Words	Babbling	Babbling	Babbling	Words	Babbling	Words	Babbling	Short phrases	Babbling	Words
Last brain MRI findings	Mild atrophy	Normal	Mild atrophy	Not tested	Normal	Normal	Normal	Normal	Normal	Mild atrophy	Normal

Physical examination											
Muscle tone	Hypotonia, generalized	Hypotonia, generalized	Hypotonia, generalized	Hypertonia and rigidity, generalized	Normal	Hypertonia and rigidity, generalized	Normal	Hypertonia, generalized	Rigidity, generalized	Rigidity, generalized	Hypertonia and rigidity, generalized
Ataxia	(−)	(−)	Appendicular, axial, gait	Appendicular, axial, gait	(−)	Appendicular, axial, gait	(−)	(−)	Appendicular, axial, gait	Appendicular, axial, gait	Appendicular, axial, gait
Dystonia	(−)	(−)	(−)	(−)	(−)	Four extremities	(−)	(−)	(−)	(−)	(−)
Scoliosis	Mild	Mild	(−)	(−)	Mild	Mild	(−)	(−)	Mild	(−)	Moderate
Pes planovalgus	(+)	(+)	(−)	(−)	(−)	(−)	(−)	(+)	(−)	(+)	(+)
Restriction of dorsiflexion of ankle	(+)	(+)	(+)	(+)	(−)	(+)	(+)	(+)	(+)	(+)	(+)

MECP2, methyl-CpG-binding protein 2; Arg, arginine; Cys, cysteine; Ter, termination codon; Thr, threonine; Met, methionine; Pro, proline; y, year; mo, month; VPA, valproic acid; LEV, levetiracetam; LCM, lacosamide; ZNS, zonisamide; PB, phenobarbital; CBZ, carbamazepine; LTG, lamotrigine; MRI, magnetic resonance imaging

Table 2. Spatiotemporal gait parameters in patients with Rett syndrome and female controls

	Patients with Rett syndrome (n=11)	Healthy controls (n=33)	*P* value
Age, years [a]	9 [5–18]	9 [7–14]	0.789
Height, cm [b]	1.22 (0.14)	1.33 (0.11)	0.011
Weight, kg [a]	18.1 [14.6–40.9]	26.2 [19.8–53.9]	0.031
Length of lower extremities, cm [b]	0.62 (0.087)	0.65 (0.062)	0.147
Walking speed, m/second [b]	0.66 (0.22)	1.13 (0.14)	<0.001
Step length/length of lower extremities [b]	0.56 (0.17)	0.81 [0.70-0.97]	<0.001
Cadence, steps/minute [b]	114 (20)	126 (9.7)	0.014
Step width, m [b]	0.20 (0.063)	0.10 (0.024)	<0.001

Coefficients of variation of the step length [a]	0.18 [0.08–0.52]	0.05 [0.01–0.15]	<0.001

[a] Data were analyzed using the Mann–Whitney U test; results are presented as median [range].

[b] Data were analyzed using the two-sample t-test; results are presented as mean (standard deviation).

Table 3. Comprehensive indices of gait kinematics in patients with Rett syndrome and female controls

	Patients with Rett syndrome (n=11)	Healthy controls (n=33)	*P* value
Gait Deviation Index, points	72.6 (7.5)	95.2 (8.8)	<0.001*
Gait Profile Score, °	10.9 [7.7–15.8]	5.9 [4.2–9.7]	<0.001
Gait Variable Scores, °			
Pelvic tilt	3.2 [1.1–10.3]	3.0 [0.5–13.1]	<0.001
Pelvic obliquity	3.4 [1.3–4.7]	1.2 [0.4–3.3]	<0.001
Pelvic rotation	5.6 [1.5–11.6]	2.2 [1.0–4.1]	<0.001
Hip flexion-extension	9.7 [5.7–16.9]	4.8 [1.3–15.8]	<0.001
Hip abduction-adduction	5.8 [3.3–10.2]	3.3 [2.1–4.6]	<0.001
Hip rotation	9.0 [2.8–22.6]	8.3 [2.5–15.8]	0.915
Knee flexion-extension	11.0 [6.8–14.8]	4.7 [2.3–14.9]	<0.001

Ankle dorsiflexion-plantarflexion	8.6 [6.3–31.0]	3.8 [2.1–6.1]	<0.001
Foot progression angle	13.8 [5.5–28.9]	7.0 [3.4–17.5]	0.013

* Data were analyzed using the two-sample t-test; the results are presented as mean (standard deviation).

All other variables were analyzed using the Mann–Whitney U test; results are presented as median [range].

The gait profile score was composed of nine gait variable scores, as shown in this table.