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The associated factors of nutritional issues and body composition in Rett syndrome

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ABSTRACT

Individuals with Rett syndrome (RTT), a rare neurodevelopmental disorder, often face significant nutritional challenges. We explored factors affecting nutritional status and body composition in RTT individuals using dietary assessments and bioelectrical impedance analysis (BIA). This study involved 40 participants and found that underweight individuals with severe growth deficits often had reduced body fat, visceral fat, and arm circumference. Protein and zinc intake percentages were significantly lower in those with higher severity scores. Adolescents with the highest growth deficit and underweight ratios had caloric, protein, and calcium intakes below the Dietary Reference Intakes (DRI). Over 88 % of adults had insufficient calcium, magnesium, iron, zinc and fiber intake. Among the 15 females with RTT, sarcopenia was present in 14 (93.3 %), while sarcopenic obesity was present in 4 (26.67 %). Therefore, comprehensive dietary and body composition assessments, including body mass index, body fat, skeletal muscle, and mid-upper arm circumference, are crucial for identifying nutritional disorders in RTT. Addressing these issues through appropriate interventions is essential for improving nutritional management and outcomes for individuals with RTT.

1. Introduction

Rett syndrome (RTT) is primarily caused by mutations of methyl CpG-binding protein 2 (MECP2), a rare neurodevelopmental disease. The clinical manifestations include feeding difficulties, respiratory-related illness, impaired bone health (scoliosis/osteopenia), and gastrointestinal dysmotility [1]. They also have lipid metabolism problem, immune dysfunction, neurological impairment, and growth deficits [2,3]. The potential risk factors of respiratory infection in individuals with RTT include epilepsy, scoliosis, poor oromotor control, walking status, and clinical severity of RTT [4].There are various factors affecting growth deficits, including the type of genetic defect, clinical disease severity, gastrointestinal disease, feeding difficulties, and nervous system disorders [5,6]. Growth deficits may decrease with age. However, they increase significantly with other factors, such as small body size, reduced bone mineral content, fracture susceptibility, and gastrostomy use.

The major dysphagia problems in RTT individuals are limited to oral preparatory phases, including dystonic and dyskinetic tongue movements (involuntary tongue retroflexions), prolonged oral stage, and poor bolus formation [7,8]. The insufficient dietary intake in RTT may increase the risk of malnutrition. Recent researches demonstrated that the significantly insufficient intake of protein in RTT may lead to severe growth deficit [3]. Low nutrient intake in RTT due to limited texture tolerance for chewy and crunchy foods, and lack of self-feeding in RTT may also contribute to growth deficits [9]. Therefore, customized recommendations and modifications in food texture, such as gummy foods and pureed foods, may improve energy and nutrients intake to meet the requirements.

In recent years, the attention to the issues of sarcopenia and sarcopenic obesity, defined as low skeletal muscle mass accompanied by excess body fat, has been increased. Motil et al. found that while

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sleeping and resting RTT individuals' metabolic rates were 23 % lower than those of healthy girls, they were similar to those of healthy girls in active waking [10]. They also found that the involuntary hand movements of RTT girls do not increase in total daily energy expenditure and there was significantly less lean body mass instead of body fat compared to healthy girls of the same age. Previous research had shown that the girls with RTT would first sacrifice their lean body mass to maintain their body fat [11]. Therefore, the low muscle mass may increase metabolic syndrome risk, and decreased bone strength in individuals with RTT [12]. The treatments for sarcopenic obesity are implemented by lifestyle modified-diet and exercise, including calorie restriction and the increase of protein, calcium, and vitamin D supplement [13].

However, there is little specific guidance on the impact of disease severity and body composition parameters on nutritional status in RTT. International expert consensus recommends dual-energy X-ray absorptiometry (DXA) for body composition assessment, with bioelectrical impedance analysis (BIA) as a secondary option. This study chose BIA for its convenience and cost, although its accuracy may decline in cases of severe obesity or fluid changes. In contrast, DXA is costly and less reliable for obese individuals, and to sedate patients for DXA may be difficult for individuals with RTT. Therefore, this research explored the associated factors of nutritional issues and body composition in RTT individuals in Taiwan through dietary assessment and BIA measurements.

2. Materials and methods

This study was approved by the Institutional Review Board of National Taiwan University Hospital. Individuals, who met the clinical diagnostic criteria for RTT, were enrolled. The clinical severity and dystonia status were evaluated by two pediatric neurologists using the Clinical Severity Score (Percy scale) and Burke-Fahn-Marsden-movement scale (BFMMS) [14,15]. The Severity Score consists of multiple questions concerning growth, motor, scoliosis, language, respiratory dysfunction and epilepsy condition. The BFMMS was applied to assess the severity of dystonia. The higher scores demonstrate greater severities.

Individuals with RTT were evaluated and followed up at the Integrated Rett Syndrome Clinic at National Taiwan University Children's Hospital (NTUCH), when individuals participated in nutritional consultation and anthropometric measurement. The complete nutritional assessment was undertaken twice annually. Dietary questionnaires were completed by registered dietitian. Assessment of usual dietary pattern, food consistency and preferences, and length of typical mealtime were recorded by the dietitian. The evaluations of nutrient intakes were determined by the 24-h diet recall and 3-day food records. Caregivers recorded the type and quantity of foods, beverages, and supplements, and some caregivers used electronic scale to measure food quantity. The dietary records were confirmed again with the food models and were filled up the details of the records. In our study, in addition to having caregivers to record their diet for three days, we also incorporated a digital 24-h dietary recall and food weighing methods to reduce errors in estimating food portions, and some caregivers documented dietary intake with a digital 24-h recall and food weighing methods to minimize errors in portion size estimation.

The assessment of dietary intake, including energy, carbohydrate, protein, fat, micronutrients content of foods and supplements, were analyzed by the database of food analysis and the manufacturers' label in Taiwan. The nutrient intakes were compared with the Dietary Reference Intakes (DRIs) criterion for Taiwanese (8th edition) (Administration, 2020). The laboratory analysis of nutritional status was all performed.

Anthropometric measurements were done about every 3~6 months by a fixed stadiometer or seat-type weighing scale. The cut-points of underweight or obesity were set by body mass index (BMI) with the age-specific percentile reference in Taiwan [16]. Adult body weight standards from the Ministry of Health and Welfare in Taiwan: Underweight is BMI < 18.5 kg/m^2, overweight is BMI 24–27 kg/m^2, and obesity is BMI > 27 kg/m^2. Body composition was predicted using an In Body S10 device. This device is adopted in the BIA with multi-frequency technique using equations based on impedance, age, height, and weight. The individual was sitting on a chair with legs apart and arms not touching. The measurement values included the percent of body fat (PBF) and fat free mass (FFM). The Fat Free Mass Index (FFMI) was defined as FFM (kg) divided by the height squared (m^2); the Appendicular Skeletal Muscle Index (ASMI) was defined as the upper and lower limb skeletal muscle mass (kg) divided by the height squared (m^2). Sarcopenia was defined as ASMI< 5.7 kg/m^2 by BIA in females [17]. The sarcopenic obesity was defined as ASM/Weight (ASMR) < 25.7, BMI$\geqq$25 kg/m^2 and VFA$\geqq$100 cm^2 in adult female (Chen et al., 2017). Besides, the pediatric sarcopenia was characterized by reduced appendicular skeletal muscle mass lower than the sex- and age-specific 3rd percentiles reference values [18]. Malnutrition in adults was defined based on either a low BMI ($<$18.5 kg/m^2) or combined unintentional weight loss and at least either reduced BMI or FFMI$<$15 kg/m^2 in female [19]. All methods were carried out in accordance with relevant guidelines and regulations of our hospital. Informed consent was obtained from their caregivers as parts of the evaluation in the Integrated Rett Syndrome Clinic.

2.1. Statistical analysis

Results were expressed as mean, standard deviation (SD), number of cases, and percentage. The data were shown as means ± SD. Statistical analysis was done using independent T-test, Chi-square test, Fisher's exact test for comparing categorical variables. Statistical difference was significant at $p < 0.05$. The Logistic regression for the effect of different characteristics of RTT with an individual's underweight was also done. Data were analyzed using SAS 9.4.

3. Results

3.1. Nutritional assessment

Total 40 individuals with RTT were done for the nutritional assessment and growth measurements by age groups in Table 1. Dietary energy intake consisted of 50.3 %–51.6 % in carbohydrates, 32.8 %–34 % in fat, and 15.4 %–16.8 % in protein, with no significant differences among age groups. Energy intake below DRI criterion varied in 3 groups (81.81 % in children, 100 % in adolescents, and 72.22 % in adults, $p = 0.1655$) without significant difference. There was also no significant difference in protein intake below DRI in 3 groups (9.09 % in children, 54.55 % in adolescents, and 27.78 % in adults, $p = 0.0755$). However, the DRI percentage was significantly lower in the 8–18 age group for energy intake (73.82 ± 10.46, $p = 0.0099$) and protein intake (110.65 ± 29.94, $p = 0.0004$). The BMI was also significant lower in the 8–18 age group (14.79 ± 2.58, $p = 0.0003$). Severe growth deficits (45.45 %, $p = 0.2329$) and underweight (63.64 %, $p = 0.2637$) were also most common in this age group, without significant differences (Table 1).

Calcium and iron insufficient intake exceeded 72.73 % across age groups, showing no significant differences ($p = 0.1478$ for calcium and $p = 0.4078$ for iron). Adults exhibited significantly higher proportions of insufficient magnesium (88.89 %, $p = 0.0125$) and zinc (100 %, $p < 0.0001$) intake (Fig. 1). Lastly, only one individual out of 40 met the DRI criterion for dietary fiber intake.

3.2. Nutritional assessment and disease severity

Total 37 individuals were evaluated with the Clinical Severity Score to assess the disease severity (Table 2). The percentage of severe growth deficit was significantly higher in those with higher score ($p = 0.0023$). The DRI percentage for age of dietary protein and zinc intakes were

Table 1
Nutritional assessment of the cohort by age group.

	0~8y (N = 11)	8~18y (N = 11)	≥18y (N = 18)	P-Value
Age(y), Mean (SD)	4.81 (1.55)	11.56 (3.29)	27.23 (6.99)	<0.0001
Growth Deficit, n (%)				0.2329
Mild	7 (63.64)	3 (27.27)	5 (27.78)	
Moderate	3 (27.27)	3 (27.27)	8 (44.44)	
Severe	1 (9.09)	5 (45.45)	5 (27.78)	
Head Circumference (cm), Mean (SD)	47.14 (3.53)	49.58 (1.49)	51.33 (2.29)	0.0005
BMI (Body Mass Index, kg/m^2), Mean (SD)	15.21 (2.44)	14.79 (2.58)	20.15 (4.57)	0.0003
Underweight, n (%)	2 (18.18)	7 (63.64)	6 (33.33)	0.2637
Normal Weight, n (%)	6 (54.55)	3 (27.27)	7 (38.89)	
Overweight, n (%)	2 (18.18)	1 (9.09)	5 (27.78)	
Obesity, n (%)	1 (9.09)	0 (0.00)	0 (0.00)	
Nutrients intake, Mean (SD)				
Energy (Kcal)	1181.00 (269.29)	1344.82 (149.57)	1349.78 (214.94)	0.1074
Protein (% E)	15.42 (2.38)	15.55 (2.52)	16.81 (2.30)	0.2204
Carbohydrate (% E)	50.55 (9.07)	51.59 (7.45)	50.33 (7.89)	0.9179
Fats (% E)	34.03 (8.31)	32.86 (7.23)	32.86 (8.52)	0.9211
Saturated Fats (% E)	10.86 (2.91)	9.57 (5.32)	9.39 (3.87)	0.6256
Protein (g)	45.79 (13.39)	52.15 (9.57)	56.44 (9.89)	0.0487
Carbohydrate (g)	148.38 (38.25)	173.50 (31.55)	168.52 (33.96)	0.1984
Fats (g)	41.46 (17.85)	48.25 (12.67)	51.52 (17.79)	0.2957
Saturated Fats (g)	14.60 (6.60)	14.18 (7.30)	14.40 (7.05)	0.9902
Dietary Fiber (g)	7.32 (4.02)	10.65 (5.03)	10.12 (5.52)	0.2440
Calcium (mg)	501.18 (251.01)	538.55 (262.06)	630.50 (334.75)	0.4841
Magnesium (mg)	153.00 (47.26)	179.73 (61.69)	191.22 (78.35)	0.3345
Phosphate (mg)	673.36 (172.87)	779.36 (172.56)	767.11 (191.71)	0.3171
Iron (mg)	7.76 (2.41)	8.45 (4.33)	8.29 (5.38)	0.9297
Zinc (mg)	6.35 (1.54)	6.86 (2.03)	7.09 (1.30)	0.4731
DRI %, Mean (SD)				
Energy	84.28 (13.45)	73.82 (10.46)	89.61 (13.54)	0.0099
Protein	168.92 (57.83)	110.65 (29.94)	111.78 (20.20)	0.0004
Calcium	89.56 (54.81)	55.35 (24.17)	62.17 (33.81)	0.0956
Magnesium	144.54 (67.81)	83.38 (37.65)	59.63 (24.57)	<0.0001
Phosphate	142.78 (44.35)	104.42 (32.76)	93.75 (24.61)	0.0016
Iron	77.57 (24.08)	71.17 (47.14)	55.21 (35.80)	
Zinc	127.01 (31.04)	95.93 (52.02)	59.20 (10.88)	<0.0001
<DRI Criterion, n (%)				
Energy	9 (81.81)	11 (100.00)	13 (72.22)	0.1655
Protein	1 (9.09)	6 (54.55)	5 (27.78)	0.0755
Calcium	8 (72.73)	11 (100.00)	16 (88.89)	0.1478
Magnesium	4 (36.36)	8 (72.73)	16 (88.89)	0.0125
Phosphate	2 (18.18)	6 (54.55)	11 (61.11)	0.0690
Iron	8 (72.73)	8 (72.73)	16 (88.89)	0.4078
Zinc	3 (27.27)	7 (63.64)	18 (100.00)	<0.0001
Dietary Fiber	11 (100.00)	11 (100.00)	17 (94.44)	1.0000
Carbohydrate (<50 %E-AMDR), n (%)	5 (45.45)	5 (45.45)	8 (44.44)	1.0000
Saturated Fats (>10 %E-AMDR), n (%)	7 (63.64)	5 (45.45)	7 (38.89)	0.5124

Abbreviations: Descriptive Statistic (Mean, Standard Deviation, Number of Cases, Percentage).

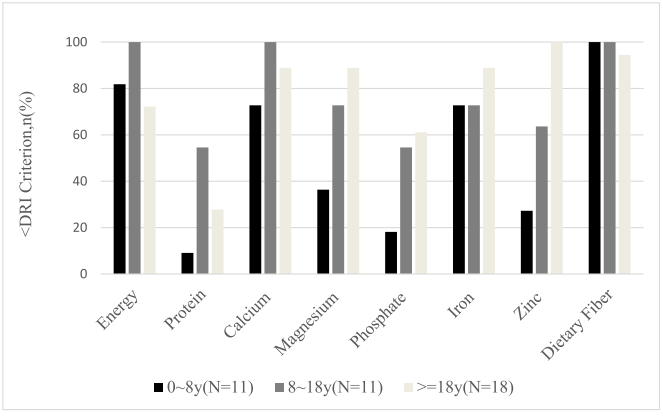

Fig. 1. Proportions of intake below Dietary Reference Intake (DRI) standards. Adults exhibited significantly higher proportions of insufficient magnesium (88.89 %, p = 0.0125) and zinc (100 %, p < 0.0001) intake.

significantly lower in RTT with higher severity score (p = 0.0306 for protein and p = 0.0236 for zinc). The percentage of zinc intake < DRI criteria was also significantly higher in those with higher score (p = 0.0263). The DRI percentage of energy intake was lower in individuals with severe disease without significance (88.87 vs. 81.04 %, p = 0.0819). No significant differences were observed for other micronutrients, including calcium, magnesium, phosphate, and iron.

3.3. Body composition

A total of 29 individuals was evaluated for body composition by BIA. The body composition, motor and severity scores of cohorts by age group were shown in Table 3. Significant differences were found in FMI (p = 0.0033), PBF (p = 0.0086), FFMI (p = 0.0345), and ASMI (p = 0.0123) among age groups, indicating variations in body fat and skeletal muscle measurements. Notably, sarcopenic issues were prevalent in adolescents (100 %) and adults (93.33 %) (p = 0.0276). Although the percentage of sarcopenic obesity was higher in adult group (26.67 vs. 12.50 %, p = 0.4542), it was not statistically significant (Fig. 2). However, the waist circumference was significantly higher in adult group (Table 3, p < 0.0001).

In adult group with RTT (mean age 28.07 ± 7.19 years), the higher

Table 2
Nutritional assessment of the cohort by severity scores.

Total N = 37 (Severity Score Median = 22)	Lower Score(N = 18)	Higher Score (N = 19)	P-Value
Age(y), Mean (SD)	12.58 (9.93)	19.32 (11.18)	0.0609
Growth Deficit, n (%)			0.0023
Mild	12 (66.67)	3 (15.79)	
Moderate	5 (27.78)	7 (36.84)	
Severe	1 (5.56)	9 (47.37)	
Head Circumference(cm), Mean (SD)	49.94 (3.04)	49.37 (3.05)	0.5691
BMI (Body Mass Index, kg/m^2), Mean (SD)	17.86 (4.12)	17.31 (4.68)	0.7078
Underweight, n (%)	4 (22.22)	8 (42.11)	0.4725
Normal Weight, n (%)	8 (44.44)	8 (42.11)	
Overweight, n (%)	5 (27.78)	3 (15.79)	
Obesity, n (%)	1 (5.56)	0 (0.00)	
Osteopenia, n (%)	1 (6.25)	2 (13.33)	0.5996
Sarcopenia, n (%)	11 (61.11)	12 (92.31)	0.3333
Sarcopenic Obesity, n (%)	2 (13.33)	3 (23.08)	0.6389
Nutrients intake, Mean (SD)			
Protein (% E)	15.49 (2.28)	16.58 (2.59)	0.1853
Carbohydrate (% E)	49.79 (8.55)	51.63 (7.95)	0.5033
Fats (% E)	34.72 (8.76)	31.80 (7.58)	0.2846
Saturated Fats (% E)	10.46 (3.15)	10.00 (4.43)	0.7217
Energy (DRI %)	88.87 (11.59)	81.04 (14.71)	0.0819
Protein (DRI %)	146.47 (52.11)	114.67 (28.44)	0.0306
Calcium (DRI %)	60.86 (47.93)	70.79 (34.24)	0.4714
Magnesium (DRI %)	94.90 (56.97)	88.77 (57.61)	0.7471
Phosphate (DRI %)	117.66 (45.63)	106.38 (31.65)	0.3862
Iron (DRI %)	65.13 (29.41)	65.32 (42.64)	0.9877
Zinc (DRI %)	106.83 (51.86)	73.89 (26.57)	0.0236
<DRI Criterion, n (%)			
Energy	14 (77.78)	16 (84.21)	0.6928
Protein	3 (16.67)	7 (36.84)	0.2691
Calcium	16 (88.89)	16 (84.21)	0.6774
Magnesium	13 (72.22)	13 (68.42)	0.8004
Phosphate	7 (38.89)	10 (52.63)	0.4018
Iron	14 (77.78)	16 (84.21)	0.6928
Zinc	9 (50.00)	16 (84.21)	0.0263
Dietary Fiber	18 (100.00)	19 (100.00)	NA
Carbohydrate (<50 %E-AMDR), n (%)	8 (44.44)	9 (47.37)	0.8584
Saturated Fats (>10 %E-AMDR), n (%)	10 (55.56)	8 (42.11)	0.4018

Abbreviations: Subjects Classified into Two Group by Median Severity Score. Significance Tests Were Based Upon Independent T Test, Chi-Square Test, Fisher's Exact Test.

dystonia (45.07 ± 19.55, p = 0.0234) and severity scores (23.64 ± 6.97, p = 0.1366) were observed. Although the mean values for VFA (116.18 ± 58.94 cm^2, p = 0.0006), PBF (39.14 ± 10.34 %, p = 0.0086), FFMI (12.25 ± 1.55 kg/m^2, p = 0.0345), and ASMI (3.81 ± 0.99 kg/m^2, p = 0.0123) were significantly higher in adult group, only 4 individuals (26.67 %, p = 0.4542) met the diagnostic criteria for sarcopenic obesity in adult group. These proportions were not significantly different from those in children and adolescents.

In the 8–18 years age group (mean: 11.83 ± 4.17 years), mean values for FFM (21.38 ± 4.80 kg), SMM (10.32 ± 2.87 kg), ASMI (3.1 ± 0.82 kg/m^2), and ASMR (20.23 ± 5.06) fell below the 3rd percentiles. All individuals met the pediatric sarcopenia criteria [18] (p = 0.0276). In those under 8 years old (mean age: 5.25 ± 1.98 years), mean values for FFM (13.8 ± 5.29 kg), SMM (5.9 ± 3.04 kg), ASMI (2.48 ± 0.96 kg/m^2), and ASMR (16.08 ± 5.03) were below the 3rd percentiles, with 50 % meeting pediatric sarcopenia criteria. Additionally, in both age groups (8–18 years and <8 years), mean PBF (27.80 % vs. 26.07 %) and FMI (4.43 vs. 4.10 kg/m^2) met the 25-50th percentiles for Chinese children and adolescents [20].

3.4. Body composition and dystonia severity

Based on the medium value of the dystonia severity scale (BFMMS), it was classified into lower and higher score groups (Table 4). In lower and higher BFMMS score groups, significant differences were observed in mean age (10.80 ± 8.34 vs. 25.54 ± 8.71 years, p = 0.0001), body height (124.70 ± 20.84 vs. 143.90 ± 8.28 cm, p = 0040), body weight (26.79 ± 13.91 vs. 41.81 ± 10.83, p = 0.0041), BMI (16.19 ± 3.78 vs. 20.12 ± 4.69 kg/m^2, p = 0.0212), and body fat percentage (28.58 ± 9.63 % vs. 38.38 ± 11.15 %, p = 0.0192) (Table 4). However, regression analysis revealed no statistically significant differences in body fat percentage with respect to age, body height, body weight, and body mass index (BMI) in the studied individuals (p = 0.5181). Additionally, disease severity scores (16.33 ± 6.85 vs. 25.00 ± 6.72, p = 0.0029) and dystonia (0.20 ± 0.41 vs. 1.42 ± 1.51, p = 0.0182) were significantly higher in adults compared to younger individuals. However, no significant differences were observed in lean body mass between the groups (p = 0.1039 for ASMI and p = 0.7990 for ASMR).

3.5. Body composition and underweight

Total 29 subjects were categorized as non-underweight and underweight (<5th percentile on BMI) for comparison in terms of body composition, motor function, and severity scores (Table 5). Significant lower values were observed in BMI (19.62 ± 4.45 vs. 14.57 ± 2.18 kg/m2, p = 0.0003), PBF (37.33 ± 10.33 % vs. 24.38 ± 7.23 %, p = 0.0022), VFA (95.81 ± 6.00 vs. 43.88 ± 21.85 cm2, p = 0.0030), and AC (23.66 ± 5.15 cm vs. 19.90 ± 2.61 cm2, p = 0.0492) in underweight group (Table 5). Dystonia and severity scores showed no significant differences between the groups. Regression analysis indicated that individuals with underweight and severe growth deficit were more likely to experience a decrease in PBF and VFA (OR = 0.737, p = 0.0304 for PBF and OR = 0.939, p = 0.0447 for VFA) (Table 6).

4. Discussion

In recent years, increasing attention has been paid to the problems of obesity or sarcopenic obesity in individuals with mobility difficulties or neurological damage. Our cohort findings showed that 27.3 % of young children and 27.8 % of adults met the criteria for overweight and obesity by BMI category. Considering the differences in body types among ethnicities, we adopted the definition of sarcopenic obesity for elderly females as defined by a study from Taiwan (Chen et al. in 2017); that is ASMR < 25.7, BMI > 25 kg/m^2, and VFA > 100 cm^2. Among the 15 RTT females, 4 (26.67 %) met this standard. If we were to use the standards from the Korean study proposed in the 2022 ESPEN guidelines (ASMR < 32.2 and BF > 36.5 %), then 9 (60 %) would be classified as sarcopenic obesity. Therefore, it is not suitable to adopt the standards for young adults [21]. International expert consensus recommends dual-energy X-ray absorptiometry (DXA) for body composition assessment, with BIA as a secondary option. Our study chose BIA for its convenience and cost, although its accuracy may decline in cases of severe obesity or fluid changes. To reduce biases from BIA devices, we implemented annual simplified BIA assessments for patient self-comparison. Additionally, measuring mid-upper arm circumference (MUAC) offers a quick way to assess changes in skeletal muscle mass. This method aligns with the 2022 ESPEN guidelines for diagnosing sarcopenic obesity. The presence of sleep or motor and coordination difficulties may increase risk of overweight and obesity [22]. Insufficient physical activity in children with RTT may be associated with increased risk of obesity. It is recommended that regular exercise at least 3 times a day with 15 min walking will improve lung health, metabolic rate, and weight control in RTT [23]. However, assessing physical activity intensity in RTT patients is challenging, leading to potential estimation bias in their nutritional needs. Future research could use video recordings of physical activity and muscle strength, along with activity logs, to better understand their actual needs. Studies show a correlation between muscle strength and sarcopenic obesity, highlighting the importance of accurate assessments.

Most of our cohort children were diagnosed with pediatric

Table 3
Body composition, motor and severity scores of the cohort by age group.

Total N = 29	0~8y (N = 8)	8~18y (N = 6)	≥18y (N = 15)	P-Value
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (y)	5.25 (1.98)	11.83 (4.17)	28.07 (7.19)	<0.0001
Height (cm)	111.56 (17.24)	137.20 (14.03)	144.33 (7.29)	<0.0001
Body Weight (kg)	19.63 (8.74)	29.33 (8.26)	43.31 (11.15)	<0.0001
BMI (Body Mass Index, kg/m^2)	15.18 (2.83)	15.35 (2.08)	20.67 (4.50)	0.0024
FAT Mass (kg)	5.83 (4.03)	7.95 (3.93)	17.73 (7.89)	0.0004
FMI (FAT Mass Index, kg/m^2)	4.43 (2.25)	4.10 (1.46)	8.47 (3.62)	0.0033
PBF (Percent Body Fat, %)	27.80 (10.03)	26.07 (6.60)	39.14 (10.34)	0.0086
VFA (Visceral Fat Area, cm^2)	38.99 (23.05)	42.75 (20.96)	116.18 (58.94)	0.0006
FFM (Fat Free Mass, Kg)	13.80 (5.29)	21.38 (4.80)	25.59 (5.04)	<0.0001
FFMI (Fat Free Mass Index, kg/m^2)	10.74 (0.94)	11.25 (0.87)	12.25 (1.55)	0.0345
SMM (Skeletal Muscle Mass, kg)	5.91 (3.04)	10.32 (2.87)	12.81 (3.12)	0.0001
ASM (Appendicular Skeletal Muscle Mass, kg)	3.30 (2.14)	6.09 (2.67)	8.10 (2.80)	0.0012
ASMI (Appendicular Skeletal Muscle Index, kg/m^2)	2.48 (0.96)	3.10 (0.82)	3.81 (0.99)	0.0123
ASMR (Appendicular Skeletal Muscle Mass Weight Ratio)	16.08 (5.03)	20.23 (5.06)	18.66 (3.39)	0.1896
AC (Arm Circumference, cm)	18.34 (2.97)	20.27 (2.23)	25.60 (4.20)	0.0002
Waist Cir. (cm)	53.96 (5.69)	61.77 (6.01)	76.99 (13.16)	<0.0001
Sarcopenia, n (%)	4 (50.00)	6 (100.00)	14 (93.33)	0.0276
Sarcopenic Obesity, n (%)	1 (12.50)	0 (0.00)	4 (26.67)	0.4542
Burke-Fahn-Marsden-Movement Scale (BFMMS)				
Eyes	0.06 (0.18)	0.08 (0.20)	0.14 (0.31)	1.0000
Mouth	0.31 (0.26)	1.08 (1.16)	2.57 (1.54)	0.0087
Swallow	0.38 (0.52)	0.33 (0.52)	0.29 (0.61)	0.5289
Neck	0.31 (0.7)	7.67 (10.61)	13.14 (8.22)	0.0004
Arm	0.50 (0.93)	7.82 (9.44)	13.75 (7.83)	0.0004
Leg	3.00 (1.93)	8.00 (7.90)	16.29 (1052.00)	0.0313
Trunk	0.88 (2.10)	4.17 (3.97)	8.93 (5.40)	0.0051
Sum	5.44 (3.76)	22.58 (19.73)	45.07 (19.55)	0.0234
Severity Scores				
Age Regression	2.38 (1.19)	2.33 (0.82)	3.14 (1.02)	0.0524
Somatic Growth	1.00 (1.41)	2.67 (1.75)	0.93 (1.59)	0.2979
Head Growth	1.13 (1.81)	0.67 (1.21)	2.21 (2.01)	0.1948
Motor	0.25 (0.46)	0.67 (0.52)	1.07 (1.54)	0.6304
Ambulation	1.50 (1.51)	1.33 (1.86)	2.00 (1.71)	0.5915
Hand Use	1.88 (1.13)	1.50 (1.05)	2.43 (1.09)	0.8992
Scoliosis	0.38 (0.52)	1.50 (1.05)	2.71 (1.54)	0.0063
Language	3.13 (0.99)	2.50 (1.22)	3.29 (0.99)	0.1716
Nonverbal Communication	0.88 (0.83)	0.33 (0.82)	1.00 (0.96)	0.5878
Respiratory Dysfunction	0.63 (0.52)	0.67 (1.21)	0.29 (0.47)	0.0732
Autonomic Symptoms	0.75 (0.71)	1.17 (1.17)	1.50 (1.16)	0.5089
Stereotypies	1.75 (0.71)	2.33 (1.37)	2.79 (0.80)	0.1031
Epilepsy	0.00 (0.00)	1.00 (1.67)	0.36 (0.63)	0.5033
Total Severity	15.63 (6.39)	18.67 (8.91)	23.64 (6.97)	0.1366

Abbreviations: Descriptive Statistic (Mean, Standard Deviation, Number of Cases, Percentage).

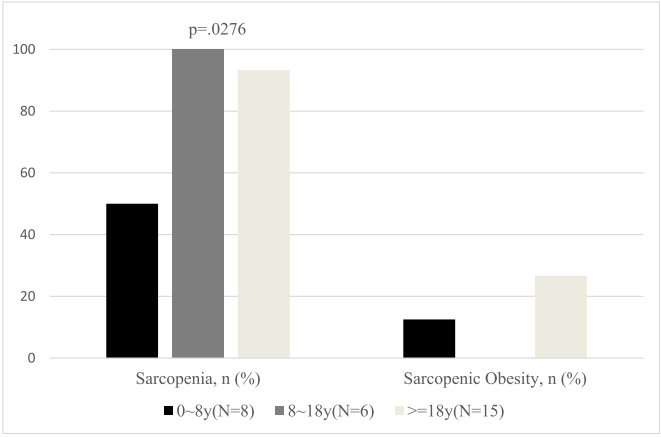

Fig. 2. Prevalence of sarcopenia and sarcopenic obesity by age group. Although the percentage of sarcopenic obesity was higher in adult group, it was not statistically significant.

sarcopenia, whose skeletal muscle mass was lower than the sex-specific and age-specific 3rd percentiles reference values [18]. The highest severe growth and underweight ratio were more prevalent in children and adolescents in our RTT cohort. Moreover, individuals' underweight with severe growth deficit was more likely to show a decrease in body fat, visceral fat and arm circumference. The use of MUAC can effectively screen for malnutrition in children [24]. Measurement errors in BIA can lead to underweight children having underestimated body fat and overestimated muscle, while obese children may have overestimated body fat and underestimated muscle [25]. However, these results were similar to the previous study, which showed that lower energy requirements and lower body composition parameters (FM and FFM) may be attributed to insufficient physical activity and consumption of nutrients in CP children with higher muscle tone [26].

The nutritional supplementation and personalized diet are necessary in RTT. Increasing weight-bearing activity and intake of adequate calcium and vitamin D are the first steps in maintaining bone health [27]. Due to dysphagia and feeding difficulties in RTT, the choice of food is severely restricted. Patients with RTT often experience chewing and swallowing difficulties. Similar to previous studies, this research indicates that improving nutritional status requires assistance in providing appropriate feeding postures and utensils. The food texture should be soft and finely mashed, or even pureed, and should be given in small bites. Additionally, the consistency of liquid foods must be adjusted based on the patient's swallowing ability [1]. There is insufficient intake of micronutrient-rich food, including zinc-rich foods such as seafood, shellfish, and red meat, and the magnesium-rich foods such as green

Table 4
Body composition of the cohort by BFMMS scores.

	Lower Score	Higher Score	P-Value
Total N = 28	(N = 15)	(N = 13)	
(BFMMS Score Median = 28.25)	Mean (SD)	Mean (SD)	
Age (y)	10.80 (8.34)	25.54 (8.71)	0.0001
Height (cm)	124.70 (20.84)	143.90 (8.28)	0.0040
Body Weight (kg)	26.79 (13.91)	41.81 (10.83)	0.0041
BMI (Body Mass Index, kg/m^2)	16.19 (3.78)	20.12 (4.69)	0.0212
FAT Mass (kg)	8.37 (6.40)	16.95 (8.48)	0.0053
FMI (FAT Mass Index, kg/m^2)	4.90 (2.52)	8.18 (4.00)	0.0140
PBF (Percent Body Fat, %)	28.58 (9.63)	38.38 (11.15)	0.0192
VFA (Visceral Fat Area, cm^2)	50.81 (37.32)	112.18 (64.62)	0.0043
FFM (Fat Free Mass, kg)	18.42 (8.07)	24.86 (3.97)	0.0243
FFMI (Fat Free Mass Index (kg/m^2)	11.34 (1.66)	11.95 (1.14)	0.2718
SMM (Skeletal Muscle Mass, kg)	8.66 (4.80)	12.32 (2.47)	0.0171
ULSMI (Upper Limb Skeletal Muscle Index, kg/m^2)	0.75 (0.35)	0.91 (0.29)	0.2139
LLSMI (Lower Limb Skeletal Muscle Index, kg/m^2)	2.22 (0.93)	2.75 (0.66)	0.0989
ASMI (Appendicular Skeletal Muscle Index, kg/m^2)	2.98 (1.20)	3.66 (0.89)	0.1039
ASMR (Appendicular Skeletal Muscle Mass Weight Ratio)	18.09 (4.85)	18.53 4.07)	0.7990
AC (Arm Circumference, cm)	20.21 (4.19)	25.06 (4.43)	0.0063
AMC (Arm Muscle Circumference, cm)	16.31 (3.63)	20.46 (3.09)	0.0034
Waist Cir.(cm)	60.44 (11.77)	75.68 (13.82)	0.0041
Severity Scores			
Age Regression	2.27 (0.88)	3.33 (1.07)	0.0090
Somatic Growth	1.40 (1.64)	1.33 (1.83)	0.9212
Head Growth	1.07 (1.71)	2.00 (1.95)	0.1978
Motor	0.20 (0.41)	1.42 (1.51)	0.0182
Ambulation	1.33 (1.45)	2.25 (1.86)	0.1624
Hand Use	1.73 (1.10)	2.50 (1.09)	0.0825
Scoliosis	1.00 (1.41)	2.83 (1.19)	0.0014
Language	2.60 (1.06)	3.58 (0.79)	0.0130
Nonverbal Communication	0.93 (0.88)	0.67 (0.98)	0.4658
Respiratory Dysfunction	0.67 (0.82)	0.25 (0.45)	0.1266
Autonomic Symptoms	0.93 (0.88)	1.50 (1.24)	0.1785
Stereotypies	2.00 (0.93)	2.83 (0.94)	0.0293
Epilepsy	0.20 (0.56)	0.58 (1.24)	0.2940
Total Severity	16.33 (6.85)	25.00 (6.72)	0.0029

Abbreviations: Subjects Classified into Two Group by Median Score. Significance Tests Were Based Upon Independent T Test, Chi-Square Test, Fisher's Exact Test.

Table 5
Body composition, motor and severity scores of the cohort by underweight group.

Total N = 29	Non-Underweight (N = 20)	Underweight (N = 9)	P-Value
	Mean (SD)	Mean (SD)	
Age (y)	18.15 (12.31)	19.00 (11.17)	0.8610
Height (cm)	131.50 (19.88)	138.90 (14.37)	0.3288
Body Weight (kg)	36.18 (15.86)	28.80 (8.56)	0.2033
BMI (Body Mass Index, kg/m^2)	19.62 (4.45)	14.57 (2.18)	0.0003
FAT Mass (kg)	14.65 (8.88)	7.48 (4.11)	0.0062
PBF (Percent Body Fat, %)	37.33 (10.33)	24.38 (7.23)	0.0022
VFA (Visceral Fat Area, cm^2)	95.81 (6.00)	43.88 (21.85)	0.0030
FFM (Fat Free Mass, kg)	21.53 (7.93)	21.32 (4.97)	0.9431
FFMI (Fat Free Mass Index (kg/m^2)	11.96 (1.52)	10.89 (0.84)	0.0599
SMI (Skeletal Muscle Index, kg/m^2)	3.42 (1.21)	3.04 (0.74)	0.4044
ULSMI (Upper Limb Skeletal Muscle Index, kg/m^2)	0.91 (0.34)	0.62 (0.13)	0.0204
LLSMI (Lower Limb Skeletal Muscle Index, kg/m^2)	2.49 (0.92)	2.44 (0.63)	0.8762
ASMI (Appendicular Skeletal Muscle Index, kg/m^2)	3.41 (1.22)	3.06 (0.73)	0.4359
ASMR (Appendicular Skeletal Muscle Mass Weight Ratio)	17.10 (4.19)	20.88 (3.67)	0.0276
AC (Arm Circumference, cm)	23.66 (5.15)	19.90 (2.61)	0.0492
Waist Cir. (cm)	69.92 (16.60)	62.09 (5.41)	0.0690
Burke-Fahn-Marsden-Movement Scale (BFMMS)			
Eyes	0.08 (0.19)	0.17 (0.35)	0.5000
Mouth	1.53 (1.68)	1.78 (1.37)	0.6992
Swallow	0.26 (0.56)	0.44 (0.53)	0.4239
Neck	2.18 (2.33)	2.28 (2.31)	0.9214
Arm	6.42 (7.65)	12.44 (11.13)	0.1051
Leg	11.05 (10.15)	10.00 (10.44)	0.8014
Trunk	5.11 (5.57)	6.67 (5.72)	0.4981
Sum	26.63 (22.82)	33.78 (26.54)	0.4689
Severity Scores			
Age Regression	2.70 (1.08)	2.88 (1.13)	0.7051
Somatic Growth	0.35 (0.67)	3.75 (0.46)	<0.0001
Head Growth	1.75 (1.92)	1.13 (1.81)	0.4358
Motor	0.80 (1.36)	0.63 (0.52)	0.6263
Ambulation	1.80 (1.79)	1.50 (1.31)	0.6726
Hand Use	1.95 (1.15)	2.38 (1.06)	0.3742
Scoliosis	1.90 (1.80)	1.50 (0.76)	0.4159
Language	3.20 (1.11)	2.75 (0.89)	0.3153
Nonverbal Communication	0.85 (0.93)	0.75 (0.89)	0.7972
Respiratory Dysfunction	0.30 (0.47)	0.88 (0.99)	0.1533
Autonomic Symptoms	1.10 (0.97)	1.50 (1.31)	0.3800
Stereotypies	2.50 (0.95)	2.13 (1.13)	0.3771
Epilepsy	0.25 (0.55)	0.75 (1.49)	0.3826
Total Severity	19.40 (8.27)	22.50 (6.61)	0.3545

Abbreviations: Significance Tests Were Based Upon Independent T Test, Chi-Square Test, Fisher's Exact Test.

vegetable and nuts. Our study showed the DRI percentage of dietary protein and zinc intakes was significantly lower in RTT with higher disease severity ($p < 0.05$). Meanwhile, the proportion of insufficient iron intake was higher in individuals with severe disease (84.21 %). Some individuals in our cohort are unable to consume milk due to lactose intolerance and are prone to be lack of calcium. Therefore, individuals with RTT are advised to take nutritional supplements, including multiple vitamin and mineral, probiotics, and nutritional formula. Recommended dietary modifications include selecting a variety of ingredients rich in micronutrients, while preparing them into easy-to-chew, bite-sized pieces or pureed foods. This should be combined with frequent small meals and oral nutrition supplementation (ONS) to replenish any potentially lacking micronutrients. Similar to the individuals with autism, the risk factors of malnutrition include restrictive eating behaviors, more limited food repertoires, feeding problems, and gastrointestinal malabsorption. The insufficient intake of vitamin, high oxidative stress, and decreased energy utilization ability are also significantly different in different autism severity. The vitamin-mineral supplementation has been shown to improve the nutritional status and oxidative stress in children with autism [28–31]. Therefore, nutritional supplements, including multiple vitamin and mineral, probiotics, and nutritional formula, may also improve the nutritional status of individuals with RTT.

The appropriate nutritional supplements (zinc, magnesium, calcium, and iron) in RTT are given to meet the individual's requirement and improvement of epilepsy. Zinc deficiency may affect normal growth, development, and maintenance of cell function. The zinc homeostasis is

Table 6
Logistic regression for the effect of different characteristics of RTT with Individual's underweight.

	Univariate Model		Multivariate Model[a]	
	OR (95 % CI)	P-Value	OR (95 % CI)	P-Value
Age(y)	1.006 (0.940–1.077)	0.8548	1.023 (0.879–1.189)	0.7726
Growth Deficit				
Mild	Ref.			
Moderate	4.875 (0.785–30.289)	0.0892	519.221 (0.382 - >999.999)	0.0895
Severe	11.375 (1.651–78.378)	0.0135	167.691 (0.847 - >999.999)	0.0576
FMI (FAT Mass Index, kg/m^2)	0.546 (0.335–0.890)	0.0153	0.523 (0.018–4.833)	0.7039
PBF (Percent Body Fat, %)	0.859 (0.762–0.967)	0.0119	0.737 (0.559–0.972)	0.0304
VFA (Visceral Fat Area, cm^2)	0.973 (0.947–1.000)	0.0474	0.939 (0.883–0.999)	0.0447
FFM (Fat Free Mass, kg)	0.996 (0.889–1.116)	0.9404	1.078 (0.088–1.309)	0.4495
FFMI (Fat Free Mass Index, kg/m^2)	0.447 (0.187–1.065)	0.0692	0.309 (0.083–1.155)	0.0809
ULSMI (Upper Limb Skeletal Muscle Index, kg/m^2)	0.010 (<0.001–0.838)	0.0415	323.542 (<0.001 - >999.999)	0.6013
LLSMI (Lower Limb Skeletal Muscle Index, kg/m^2)	0.923 (0.350–2.432)	0.8706	>999.999 (0.002 - >999.999)	0.2713
ASMI (Appendicular Skeletal Muscle Index, kg/m^2)	0.728 (0.334–1.585)	0.4238	96.705 (0.004 - >999.999	0.3694
ASMR (Appendicular Skeletal Muscle Mass Weight Ratio)	1.317 (1.012–1.713)	0.0405	1.461 (0.433–4.929)	0.5410
AC (Arm Circumference, cm)	0.809 (0.646–1.012)	0.0633	0.656 (0.430–1.001)	0.0503
Waist Cir.(cm)	0.953 (0.888–1.023)	0.1842	0.905 (0.791–1.035)	0.1453

[a] Adjusted Age, Growth Failure.

very important in regulating neuronal excitation and inhibition. The intake amount and the absorption of zinc affect zinc levels [32]. Magnesium is the essential and important nutrient acting as a cofactor in human biochemical reactions, including regulating muscle contraction, blood pressure and protein synthesis. Severe magnesium deficiency may cause epilepsy [33]. Therefore, sufficient intake of zinc and magnesium can decrease the severity of epilepsy in RTT.

The individualized complete nutritional assessments include the texture, type and quantity of consumed foods, and body composition by BIA. Regarding dietary intake for RTT, the research team collaborated with primary caregivers to develop practical meal recipes and conducts nutritional assessments and body composition analyses every six months. For several overweight patients, a calorie-restricted diet with reduced carbohydrate intake has helped with weight loss; for patients with sarcopenia, an increase in calorie and protein intake has been provided, resulting in observed improvements. Future studies will continue to explore the effects of nutritional interventions on body composition. They can provide appropriate nutritional advice, assess nutritional conditions (sarcopenia or obesity), and improve nutritional status. Experts recommend a comprehensive multidisciplinary approach for weight management in children with autism, referencing the 2007 AAP guidelines. This includes using the Food Stoplight system to guide food choices, reducing high-energy-dense snacks, and ensuring adequate intake of quality protein and micronutrients [34]. Additionally, rehabilitation therapy should promote accessible physical activity. Downs et al. suggests that regular exercise, at least three times a day for 15 min in each session, can enhance lung health, metabolic rate, and weight control, especially in individuals with RTT [23]. Dietary patterns show regional differences; however, when assessing individual nutritional status, such as caloric and nutrient intake, there is still general applicability of our study to other countries with different diet habit. The study on Polish girls with Rett syndrome found that they consumed fewer calories, fiber, and some micronutrients [35]. Thus, this research emphasizes the uniqueness of Asian dietary habits. The recommendation that RTT individuals under the age of 12 should undergo the nutritional assessment twice annually and annually thereafter had been proposed in the past [6]. Additionally, the 2017 guidelines from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend biannual assessments using methods such as height, weight, skinfold thickness, and MUAC for children with neurological disorders. Regular monitoring of growth, body composition, and micronutrient levels is crucial for determining energy and nutrient needs to ensure children neither over- nor undernourished [36]. In our cohort, initial assessments were conducted during outpatient treatment, followed by follow-ups two months later. If no malnutrition or mild risk for malnutrition was found, the next assessment would be three months later; if mild risk for malnutrition persisted, it would shift to every six months. If there is malnutrition at follow-ups, we will evaluate the individuals every month. Because our cohort, excluding one, had received Integrated Specific Clinic Care for more than 2 years, the children with higher disease severity did not show significant difference in body composition. Therefore, integrated clinic care is mandatory for individuals with RTT.

Although we followed up more than 50 % of individuals with RTT in Taiwan, the major limitation of the present study is the insufficient cases, and the complex characteristics of the group. Therefore, this should be considered in the future study involving a larger group, including other individuals in different countries.

5. Conclusions

The individuals' underweight with severe growth deficit was more likely to show a decrease in body fat, visceral fat and arm circumference. The DRI percentage of dietary protein and zinc intakes was significantly lower in RTT with higher severity score. Furthermore, the highest severe growth and underweight ratio were among children and adolescents, whose daily calorie and protein intake were below DRI criterion and whose calcium intake was also insufficient. The micronutrients intake of calcium, magnesium, iron, and zinc was 70 % lower than DRIs in adults. Although not significant, some adult cohorts are underweight while others have sarcopenic obesity. Therefore, the complete assessment of dietary intake and body composition, including the simple conventional measurement of body weight and arm circumference, may detect potential nutritional disorders for individuals with RTT. Based on our findings, there is a need to determine the physical activity on nutritional status and body skeletal muscle mass separately in RTT for better care of this specific disease group. Therefore, to develop practical meal recipes with primary caregivers may be mandatory. For example, in overweight patients, a calorie-restricted diet with reduced carbohydrate intake may help with weight loss, and for individuals with sarcopenia, an increase in calorie and protein intake may be provided, which can result in observed improvements. Over the past decade, dietary data from multiple cases have been collected, and the effectiveness of nutrition interventions will continue to be analyzed. Future studies will continue to explore the long-term effects of nutritional interventions such as targeted nutritional interventions on body composition in RTT.

Ethic approval

The study was approved by the ethics committee of National Taiwan University Hospital.

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No.

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Data availability

The datasets used during the current study were available from the corresponding author on reasonable request.

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