EATING PRACTICES, NUTRITIONAL STATUS AND CONSTIPATION IN PATIENTS WITH RETT SYNDROME

Flavia SCHWARTZMAN¹, Márcia Regina VÍTOLO², José Salomão SCHWARTZMAN³ and Mauro Batista de MORAIS⁴

ABSTRACT - Background - Disturbance in chewing, swallowing and digestive motility may predispose to feeding and nutritional abnormalities in patients with Rett syndrome. Objective - To evaluate the dietary habits, nutritional status and the prevalence of constipation in patients with classical Rett syndrome. Methods - Twenty seven female patients between the ages of 2.6 and 21.8 years were studied. The following parameters were evaluated: food register, weight, height and intestinal movement characteristics. Weight and height were compared with the National Center for Health Statistics standards. Results - The inability to ingest solid foods was observed in 80.8% of the patients. A height-to-age deficit was observed in 13 (48.1%) of the girls, being more intense in patients at stage IV. Weight-for-height deficit was found in 10 (37.0%) patients, 15 (55.6%) showed normal weight and 2 (7.4%) were overweight for their height. The median ingestion of energy, according to weight-for-height, was equal to 106.6%. Insufficient iron ingestion was observed in 63.0% and insufficient calcium in 55.6% of the patients. Constipation was verified in 74.1% of the patients and did not show a relationship with the quantity of fiber in the diet. Conclusion - Various nutritional problems, as well as, intestinal constipation were observed in these patients with Rett syndrome, and they must be considered in the multidisciplinary therapeutic planning of these individuals.


INTRODUCTION

Rett syndrome (RS) is a neurological disease with unknown etiology initially described by Dr. Andreas Rett, in 1966. The classic form of the disease affects only female children²¹¹.

Recently, a mutation in gene MeCP2 has been identified in 80% of the patients²¹, ²². The prevalence of the disease is 1:12.000 to 1:22.000 live births. It affects girls born from a normal and term gestation. Post natal period, as well as the first months of life, is apparently normal in these girls. The onset of the disease occurs between 6 and 18 months of life and stagnation of the neuropsychomotor development characterizes the initial phase of the disease. Other characteristics of RS are: acquired microencephaly, stereotyped movements and loss of purposeful hand use, respiratory problems, epilepsy, sensorial and motor deficits, nutritional deficits and scoliosis²⁷, ²¹, ²², ²⁸.

Chewing and swallowing problems, as well as gastroesophageal reflux, are frequent in this population²², ²³, ²⁴, ²⁰ and predispose them to various nutrition and feeding problems. Oral motor dysfunction and inability to self-feed have been described as factors that significantly affect the energy intake of children with cerebral palsy, which can lead to growth impairment²⁴, ²⁰, ²⁹.

Linear growth retardation and poor weight gain are common in girls with RS²⁶, ²³, ²⁹, although some may have adequate weight and, even, be overweight²⁴. The causes of the growth and weight deficit in RS are not yet very clear, but it seems to be multifactor. Some suggest it is part of the disease, while others suggest it is secondary to different factors, such as brain-based trophic influence, inadequate dietary intake, increased energy expenditure, malabsorption or metabolic disorders²³, ²⁵.

Chronic constipation is prevalent in patients with chronic non-progressive encephalopathy²⁵ and constitutes a serious problem that jeopardizes the quality of their lives even more. According to the few studies available²¹, ²⁹, the prevalence of constipation seems to be high in individuals with RS and may be due to medication, sedentary life and low intake of solid foods and liquids²⁴, ²⁵.

Because information on the nutritional aspects and the intestinal habits in RS are scarce, this study aimed at assessing the feeding characteristics, nutritional status and the prevalence of constipation in children with RS.

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METHODS

Study population
All the 27 patients with the classic Rett syndrome that have been invited to participate were included in this descriptive and transversal study. The invitation to the families was made by the neurological pediatricians of São Paulo and the Brazilian Association of Rett Syndrome (Abre-te/SP). All participants agreed to take part in the study.

Confirmation of the diagnostic disease and classification of RS were performed by neuropediatricians, based on the criteria modified by HAGBERG et al. The pubertal development was classified according to TANNER pubertal stages. Based on the assessment of the sexual development of the patients using TANNER’s stages of pubertal development and on the occurrence of menarche, the girls were classified into pre-pubertal: those with breast development in stage M1; pubertal: girls who presented breast development in stage M2 or above, but not yet menarche; and post-menarche: girls who had already had their first menstrual period.

The study was approved by the Ethical Research Committee of the Federal University of São Paulo – “Escola Paulista de Medicina” (UNIFESP-EPM), São Paulo, SP, Brazil. The parents or guardians gave their written consent.

Assessment of feeding practices related to oral motor dysfunctions
A questionnaire about current feeding practices, presence of chewing and swallowing problems, feeding skills and acceptance of some foods, according to their consistency and texture, was developed and applied to the parents. The following criteria were used to classify foods/liquids consumed by the patients:

1. Thin liquids: water, juice, plain milk; 2. Thick liquids: yogurts and smoothies; 3. Smooth pureed food: semi solid consistency without lumps such as puddings, liquefied foods and weight-for-height, using as reference, the Z score curves for the US population established by the National Center for Health Statistics (NCHS) and Center for Disease Control and Prevention. The cut-off points were -2.0 and +2.0 standard-deviations, for weight deficit and overweight, respectively. The height of the pubertal and post-menarche girls was assessed using height-for-age Z score, as well as, label information were used to calculate energy, macro and micronutrients amounts. Fiber intake was analyzed using a table that presented the amount of fiber in food determined by the method by the Association of Official Analytical Chemists (AOAC) which provides the total amount of fiber.

Energy adequacy was expressed according to energy recommendation based on 1. Body weight, 2. Expected weight for current height, and 3. Chronological age. Energy intake was considered adequate when intake was 100% or above the recommended allowance.

Macronutrients, vitamins A and C and iron were calculated based on the Recommended Dietary Allowances. Intake was considered adequate when 80% or more of the recommended allowances were met, according to age and pubertal development. Thus, for the pre-pubertal girls, the recommended energy, macro and micronutrient allowances correspondent to their age group were used. For pubertal girls who had not yet had the menarche, the allowances used were the ones for the age group 11 to 14 and, for post menarche girls, regardless of their age, the recommended values used were the ones for the age group 15 to 18 years old. For calcium, the Dietary Reference Intakes were used, considering the pubertal development, as explained above. The amount of fiber in the diet was compared to the minimum recommended allowance of the American Health Foundation, that is, age (in years) plus 5 g.

Anthropometric assessment
Anthropometric assessment included measurements of height and weight. Height and weight measurements were obtained according to JELLIFFE recommendations. Patients who could not stand were weighed in their parents’ arms and the patients’ weight was subtracted from the total. For all children, weight was measured to the nearest 0.1 kg on a standard beam scale. Subjects who were unable to stand, but who had only mild scoliosis or contractures, were placed supine on a firm surface and had their height measured by a recumbent stadiometer. For those girls with severe scoliosis, contractures or spasticity, knee height was used as alternative anthropometric measure. Knee height was measured following the method described by STEVENSON. Based on the equation proposed by him (shown bellow), reliable alternatives to recumbent length could be obtained.

Estimated stature (cm) = (2.69 x knee height) + 24.2.

In order to classify the nutritional status of the patients, their pubertal development was taken into consideration. Pre-pubertal girls were classified according to Z scores for height-for-age and weight-for-height, using as reference, the Z score curves for the US population established by the National Center for Health Statistics (NCHS) and Center for Disease Control and Prevention. The cut-off points were -2.0 and +2.0 standard-deviations, for weight deficit and overweight, respectively. The height of the pubertal and post-menarche girls was assessed using height-for-age Z score, also using the -2.0 and +2.0 cut-off points. Weight assessment of these girls was performed using Body Mass Index (BMI). BMI was interpreted according to the reference percentiles recommended by WHO and published.
by MUST et al. Values below the 5\textsuperscript{th} percentile were considered indicators of weight deficit, and values above the 85\textsuperscript{th} percentile were considered indicators of overweight. 

Assessment of intestinal habit

Intestinal habit of the patients was assessed through a questionnaire applied to the parents about presence of pain, difficulty or fear to evacuate, consistency and format of feces, frequency of evacuation and treatment for the constipation, if there was any.

Patients were considered to have chronic constipation when they evacuated hard feces, with pain or difficulty, with or without an increase in the interval between evacuations.

Hemoglobin determination

Hemoglobin concentration was determined using a portable photometer (HemoCue, Angelholm, Sweden) and a blood sample collected by thumb prick. Blood was not collected fasting.

The diagnosis of anemia was established according to the cut-off points suggested by the World Health Organization.

Statistical analysis

For statistical analysis, the software Jandel Sigma Stat for Windows (SPSS Inc, Chicago, IL, USA) was used. Differences were considered statistically significant for probability levels \(P < 0.05\). Statistical tests are presented together with the results.

RESULTS

The age of the patients (\(n = 27\)) varied from 2.6 to 21.8 years. Mean (standard-deviation) birth weight and height were 2967 ± 585 grams and 47.6 ± 2.1 centimeters, respectively. As far as their pubertal developmental, 11 (40.8\%) were pre-pubertal, 8 (29.6\%) pubertal and 8 (29.6\%) had already presented menarche.

Out of the total girls, 6 (22.2\%) walked independently, 3 (11.1\%) walked with help, 16 (59.3\%) remained seated for the whole time and 2 (7.4\%) remained lied down. Sixteen (59.3\%) had scoliosis, 18 (69.2\%) seizures and 22 (84.6\%) were on some type of medication at the time of the study.

Regarding the stage of the disease, 15 (55.6\%) were on Stage III and 12 (44.4\%) on Stage IV. Twenty-two (81.5\%) of the patients were considered therapeutic for seizures. The diet record of this patient showed that percentile adequacies in relation to the observed weight, height and in relation to the expected weight for height were not statistically significant. On the other hand, the median height-for-age Z-score was statistically lower in stage IV, compared to stage III.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Age (median and 25th and 75th percentiles), ability to walk, presence of scoliosis and anthropometric indicators according to Rett syndrome stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stages</td>
</tr>
<tr>
<td>Age (years)</td>
<td>7.2 (4.8; 10.0)</td>
</tr>
<tr>
<td>Inability to walk</td>
<td>8 (53.3%)</td>
</tr>
<tr>
<td>Presence of scoliosis</td>
<td>7 (46.7%)</td>
</tr>
<tr>
<td>Height deficit</td>
<td>5 (33.3%)</td>
</tr>
<tr>
<td>Weight deficit</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td>Height-for-age Z score</td>
<td>-1.0 (-3.7; -0.2)</td>
</tr>
</tbody>
</table>

\textsuperscript{1} Mann-Whitney test
\textsuperscript{2} Chi-square or Fisher’s exact test
\textsuperscript{3} Repeated measures together with multiple comparison Tukey’s test

One patient was on ketogenic diet at the time of the study, as therapeutic for seizures. The diet record of this patient showed that the proteins contributed with 13.7\%, lipids with 82.5\%, and carbohydrates with 3.8\% of the total calories. Regarding the remaining patients, proteins contributed from 11.1\% to 19.4\%, lipids from 22.8\% to 44.8\%, and carbohydrates from 40.1\% to 64.5\% of the total calories.

Medians (25th and 75th percentiles) of the energy intake percentile adequacies were: 1. In relation to weight observed = 111.0\% (95.4; 153.1); 2. In relation to expected weight for observed height = 106.6\% (92.7; 123.4) and 3. In relation to energy need for chronological age = 72.3\% (61.0; 84.6). Friedman’s test for repeated measures together with multiple comparison Tukey’s test showed that percentile adequacies in relation to the observed weight and in relation to the expected weight for height were not statistically different. In turn, these two estimates were greater than the percentile adequacy in relation to the chronological age, and the differences were statistically significant.
TABLE 2. Median and 25th and 75th percentiles of the percentile adjustments of energy, proteins, calcium, iron vitamin C, vitamin A, and dietary fiber intake

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Stage III (n = 15)</th>
<th>Stage IV (n = 12)</th>
<th>Mann-Whitney test</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of energy adequacy for observed weight</td>
<td>110.7 (85.2-125.2)</td>
<td>115.9 (95.6-172.2)</td>
<td>0.232</td>
</tr>
<tr>
<td>% of energy adequacy for ideal weight</td>
<td>101.2 (77.0-117.4)</td>
<td>113.2 (94.9-131.3)</td>
<td>0.180</td>
</tr>
<tr>
<td>% of energy adequacy for chronological age</td>
<td>77.9 (63.4-85.5)</td>
<td>71.8 (58.4-81.7)</td>
<td>0.575</td>
</tr>
<tr>
<td>% of protein adequacy</td>
<td>170.8 (141.9-212.1)</td>
<td>130.7 (106.8-146.7)</td>
<td>0.018</td>
</tr>
<tr>
<td>% of calcium adequacy</td>
<td>100.6 (63.4-120.4)</td>
<td>60.3 (40.5-68.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>% of iron adequacy</td>
<td>81.9 (50.5-97.8)</td>
<td>63.6 (56.1-77.0)</td>
<td>0.421</td>
</tr>
<tr>
<td>% of vitamin C adequacy</td>
<td>149.3 (72.5-343.5)</td>
<td>264.7 (160.1-520.8)</td>
<td>0.367</td>
</tr>
<tr>
<td>% of vitamin A adequacy</td>
<td>112.1 (63.5-155.8)</td>
<td>82.9 (63.7-103.2)</td>
<td>0.421</td>
</tr>
<tr>
<td>% of fiber adequacy</td>
<td>63.2 (36.6-127.5)</td>
<td>65.1 (49.1-84.7)</td>
<td>0.903</td>
</tr>
</tbody>
</table>

Protein intake was above the minimum recommended allowance in 26 patients (96.3%). Only one patient (3.7%) had protein intake below 80% of the recommended value. Concerning calcium intake, 15 patients (55.6%) had intakes 80% below the RDAs. Out of the 27 patients, 17 (63.0%) did not meet 80% of the recommendation for iron. Inadequate vitamin C intake was observed in six patients (22.2%). Fourteen patients (51.9%) had inadequate intake of vitamin. Regarding fiber intake, 21 patients (77.8%) presented intakes below the minimum amount recommended.

Table 2 shows energy, protein and other nutrients intake according to RS stages. The statistical analysis shows lower percentages of protein and calcium intake adequacy in patients on stage IV compared to patients on stage III.

The data obtained from the questionnaire about intestinal habit (Table 3) has shown that 20 patients (74.1%) presented...
intestinal habit compatible with constipation. Two (7.4%) had under control constipation, as they had been receiving treatment for constipation and were not constipated at the time of the study, and 5 (18.5%) presented normal intestinal habit. Out of the 22 patients with constipation, 6 (27%) were not receiving any type of treatment at the time of the study, 4 (18%) were treated with diet only, 5 (23%) were receiving laxatives, and 6 (27%) used suppository or sorbitol solution. One patient was under oral medication with mineral oil.

Median (and 25th and 75th percentiles) fiber intake of the 22 patients with constipation (61.0%; 32.2 and 84.7) was not statistically lower than the intake of the 5 patients without constipation (61.0%; 46.2 and 84.7; \( P = 0.659 \), Mann-Whitney test).

Out of the total 27 patients, 24 had their hemoglobin measured and 6 (25%) were anemic.

**DISCUSSION**

In this study on the nutritional status of individuals with RS, we have assessed 27 patients with typical clinical manifestation, diagnosed according to the modified\(^{29}\) HAGBERG et al.\(^{7}\) criteria. Samples of other studies that performed anthropometric assessment of RS individuals consisted of 10 to a maximum of 21 patients\(^{6, 8, 13, 14, 29}\). It is worth noticing that this large number, compared to the literature, was made possible owing to the help of the Brazilian Rett Syndrome Association and neuropediatricians of São Paulo city, who allowed their patients to take part in this study.

Given the progressive character of the disease, the age of the 15 patients (56%) on stage III was lower than the age of the 12 patients (44%) on stage IV. Twenty-two (81.5%) out of the total 27 patients were receiving, at least, one medication, more commonly anticonvulsants. It has been also observed that 22 patients (81.5%) had been hospitalized in the past.

Low height-for-age (<-2.0 standard-deviation) was diagnosed in 48.1% of the girls. Direct comparison of these results with the literature is difficult because not every author adopts the same anthropometric criteria. In any case, all other studies have found linear growth deficit in 48% to 70% of their samples\(^{6, 8, 13, 29}\). As for weight, 10 patients (37.0%) from this study had deficits, and 3 (11.1%) were overweight. In other studies, weight-for-height deficits have been observed in 50% to 60% of the patients\(^{6, 29}\), adopting a less rigorous cut-off point than in this study.

The existence of anthropometric deficits in RS has been confirmed, and height-for-age deficits prevailed in this study. On the other hand, overweight was also observed in three patients (11.1%). It is worth mentioning that the skinfold thickness of these three patients was compatible with obesity (data not shown).

Chewing and swallowing problems seem to be one of the factors that contribute, at least in part, to the anthropometric deficits observed in RS\(^{14}\). Our results have shown that almost all (26/27) of the patients were dependent to feed. Six parents (15.4%) perceived their daughters as not having any chewing and swallowing problems, even though none of these girls was able to eat solid foods. Our findings are compatible with other studies\(^{13, 14, 19, 29}\). It seems that oral motor deficits may worsen nutritional status by decreasing energy intake\(^{14, 30}\).

In our study, energy intake was assessed using different criteria because the anthropometric deficits observed could make the expression in relation to the chronological age not represent properly the needs of these individuals.

In this regard, the analysis in relation to the chronological age resulted in a median intake of 72.3% of the expected value for age, a number statistically lower than the median energy intake expressed compared to the expected weight (111.0%), and the expected weight for height (106.6%). Our results, such as those from the literature, have shown insufficient median intake for chronological age. Nevertheless, in our opinion, the median expressed in relation to the expected weight for observed height would be more useful information, because this would be the amount of energy intake expected to allow nutritional recovery of these patients.

The majority of patients in our study presented adequate calorie intake, despite their dependence to feed and their chewing and swallowing difficulties. As for qualitative analysis in relation to the macronutrients, they presented proteins, carbohydrates and lipids proportions within the accepted ranges (except one patient, who was receiving ketogenic diet).

Some nutrient intakes, such as calcium and iron must be discussed. Sixty-three per cent of the patients did not meet 80% of the recommendations for iron, with the lowest intake being observed in patients on stage IV, although the difference was not statistically significant, as observed on Table 2. We should stress that iron deficiency anemia prevalence in our population was 25.0%. On the one hand, this may be caused by an insufficient intake of iron with high bioavailability found in red meat (remember the swallowing difficulties and the lower intake of proteins by patients on stage IV compared to patients on stage III). On the other hand, diets poor in iron and iron deficiency anemia is a problem also observed in normal children and adolescents of São Paulo\(^{26}\).

Regarding calcium, insufficient intake was observed in 55.6% of the patients, with lower median adequacy in patients on stage IV (Table 2). This data may reflect a lower intake of milk and dairy products among older patients. An assumption that could lead to further studies is the increase in the proportion of patients with lower lactose absorption as they get older.

Generally speaking, these patients with RS, despite the chewing and swallowing difficulties, presented, in our opinion, adequate median energy intake, with deficits of iron, calcium, vitamin A and vitamin C intakes. This information might be used to guide food and vitamin/mineral supplementation recommendations. It has also been observed that 77.8% of the patients presented fiber intakes bellow the minimum recommendation (age + 5).

It is worth noticing the high prevalence of constipation (81.5%; 22/27) in this group. This result clearly depends on the criteria used to classify constipation in children and adolescents, and so far, there has been no consensus\(^{11}\), but it is unquestionable that constipation is a problem in RS. Median fiber intakes were similar among the patients with and without constipation. It should be pointed out that only two patients were classified as having


RESUMO — Racional — Distúrbios na mastigação, deglutição e motilidade digestiva podem predispor pacientes com síndrome de Rett à ocorrência de anormalidades nutricionais. Objetivos — Avaliar as práticas alimentares, o estado nutricional e a prevalência de constipação na síndrome de Rett clássica. Métodos — Estudaram-se 27 pacientes do sexo feminino, com idade entre 2,6 e 21,8 anos. Avaliaram-se os seguintes parâmetros: registros alimentares, peso, estatura, características do hábito intestinal. Peso e estatura foram comparados com os valores do Centro Nacional para Estatísticas da Saúde (EUA). Resultados — Incapacidade para ingerir alimentos sólidos foi observada em 80,8% das pacientes. Deficit de estatura foi observado em 13 (48,1%) meninas, sendo mais intenso nas pacientes no estágio IV. Deficite de estatura para a idade foi observado em 15 (48,1%) pacientes. Em 10 (37,0%) pacientes encontrou-se deficit de peso para a estatura, 15 (55,6%) apresentaram peso normal e duas (7,4%) sobrepeso para a estatura. A ingestão mediana de energia, segundo o peso para a estatura foi igual a 106,6%. Ingestão insuficiente de ferro foi observada em 63% e de cálcio em 55,6% das pacientes. Constipação foi verificada em 74,1% das pacientes e não apresentou relação com a quantidade de fibra alimentar na dieta. Conclusão — Observou-se elevada ocorrência de problemas nutricionais e de constipação intestinal, que devem ser considerados no planejamento terapêutico multidisciplinar destinado às pacientes com síndrome de Rett.


REFERENCES


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