Published in final edited form as:
J Pediatr Gastroenterol Nutr. 2012 September ; 55(3): 292–298. doi:10.1097/MPG.0b013e31824b6159.

Gastrointestinal and Nutritional Problems Occur Frequently Throughout Life in Girls and Women with Rett Syndrome

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Abstract

Objective—We conducted a nationwide survey to determine the prevalence of common gastrointestinal and nutritional disorders in Rett syndrome (RTT) based on parental reporting and related the occurrence of these problems to age and methyl-CpG-binding protein 2 (*MECP2*) status.

Methods—We designed a questionnaire that probed symptoms, diagnoses, diagnostic tests, and treatment interventions related to gastrointestinal and nutritional problems in RTT. The International Rett Syndrome Foundation distributed the questionnaire to 1666 family-based members and forwarded their responses for our review. We interrogated the Rare Disease Clinical Research Network database to supplement findings related to medications used to treat gastrointestinal problems in RTT.

Results—Parents of 983 RTT females (59%) responded and identified symptoms and diagnoses associated with gastrointestinal dysmotility (92%); chewing and swallowing difficulties (81%); weight deficits or excess (47%); growth deficits (45%); low bone mineral content or fractures (37%); biliary tract disorders (3%). Height, weight, and BMI z-scores decreased significantly with age; height and weight, but not BMI, z-scores were significantly lower in females with *MECP2* mutations than those without. Vomiting, nighttime awakening, gastroesophageal reflux, chewing difficulty, and choking with feeding were significantly less likely to occur with increasing age. Short stature, low bone mineral content, fractures, and gastrostomy placement were significantly

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jpgn.org).

Financial disclosures: The authors report the following financial disclosures: Dr. Motil, Skinner, Percy, Neul, Glaze, Lee, and Ms. Barrish, Lane, Geerts, Annese, and McNair receive research support from NIH (NCRR U54 RR019478, U54 HD06122). Ms. Lane receives funds from IRSF in her capacity as a medical/nursing consultant.

more likely to occur with increasing age. Chewing difficulty, choking with feeding, and nighttime awakening were significantly less likely to occur, whereas short stature was significantly more likely to occur, in females with *MECP2* mutations than those without. Diagnostic evaluations and therapeutic interventions were utilized less frequently than the occurrence of symptoms or diagnoses in the RTT cohort.

Conclusion—Gastrointestinal and nutritional problems perceived by parents are prevalent throughout life in girls and women with RTT and may pose a substantial medical burden for their caregivers. Physician awareness of these features of RTT may improve the health and quality of life of individuals affected with this disorder.

Keywords

Gastroesophageal reflux; gastroparesis; constipation; gastrostomy; low bone mineral content; cholelithiasis; growth; MECP2

Rett syndrome (RTT), a neurodevelopmental disorder caused by mutations in the methyl-CpG-binding protein 2 (*MECP2*) gene, is characterized clinically by a loss of purposeful hand use and spoken communication skills, as well as the development of stereotypic hand movements and gait abnormalities after a period of apparently normal development (1). Although more than 200 mutations have been identified, the diagnosis of classic RTT requires fulfillment of consensus clinical criteria with or without a *MECP2* mutation (2).

While neurological conditions prevail in RTT, gastrointestinal and nutritional problems have been reported less frequently in individuals with this disorder. Linear growth deficits, poor weight gain, and decreased bone mineralization characterize the clinical course of RTT (3–6). Oral motor dysfunction, swallowing difficulties, gastroesophageal reflux, and constipation have been described in a small number of individuals (7,8). Abdominal crises, primarily gastric perforations, have been reported rarely (9,10). Few reports systematically describe the magnitude of these clinical features of RTT. The paucity of evidence-based information led us to design this study to determine the prevalence of common gastrointestinal and nutritional problems in RTT based on parental reporting. We hypothesized that gastrointestinal and nutritional problems frequently affect girls and women with RTT, depending on their age and *MECP2* status. Our goal in reporting this information is to increase awareness among physicians and health care providers regarding the burden of gastrointestinal and nutritional problems in this disorder.

STUDY DESIGN

Subjects

The International Rett Syndrome Foundation (IRSF) maintains the North American RTT database which contains the demographics, diagnosis, and mutation status of individuals in the United States and Canada affected with this disorder (11). Girls and women who fulfill the clinical criteria for RTT, either classic or one of the variant forms, or those who do not meet criteria but have a mutation in the *MECP2* gene, comprise the North American RTT database. The parents of individuals listed in the North American RTT database served as the participants for this study.

Methods

Survey Questionnaire—We developed a structured questionnaire based on our experience with the gastrointestinal and nutritional problems associated with RTT (online-only Appendix, http://links.lww.com/MPG/A92). IRSF mailed the questionnaire to 1666 families within its membership in the United States and Canada whose daughters were

diagnosed with RTT. Because the mailings were conducted via bulk rate routing, IRSF did not have an accurate count of questionnaires not received by families due to faulty addresses. IRSF subsequently distributed the questionnaire six months later to families who attended the annual family conference and had not responded previously. Upon receipt of all responses, IRSF de-identified the questionnaires and forwarded the forms to us for data analysis.

The questionnaire included demographic items related to age, *MECP2* status, and estimates of height and weight; clinical symptoms and diagnoses related to common gastrointestinal and nutritional complaints; diagnostic procedures performed in response to symptoms; and medical, nutritional, and surgical interventions for each individual. The questionnaire was designed such that the parent provided a "yes," "no," or "don't know" response to all categorical questions (symptom/diagnosis present or absent, procedures performed or not performed, intervention applied or not applied). Exceptions included the age of each individual, which was categorized as one of six age-specific groups, and parental estimates of height and weight, which were used to calculate height-, weight-, and body mass index (BMI)-for-age z-scores based on standard reference data (12). Parental estimates of height, weight, and BMI measurements of females older than 20 y of age were assigned z-scores obtained at 20 y of age, based on the assumption that these individuals had achieved adult body size.

RDCRN Database—We also interrogated the Rare Diseases Clinical Research Network (RDCRN) database, a programmatic component of the National Center for Research Resources (NCRR), to supplement the survey data with additional medications used to treat gastrointestinal problems. The database contains information related to the clinical spectrum and natural history of individuals affected with RTT preparatory to the initiation of anticipated clinical trials. The data were collected by members of the RTT consortium from three primary centers and four satellite sites across the U.S. and entered electronically into the RDCRN database managed by the Data Technology Coordinating Center at the University of South Florida. The subset of data related to medication use was retrieved from the RDCRN database to complement data obtained from the questionnaire. Girls and women who were enrolled in the natural history study also were included in the North American RTT database.

This research study was designated exempt from institutional review and approval by the Institutional Review Board for Human Subject Research at Baylor College of Medicine. Informed consent was implied based on the return receipt of the questionnaire.

Data Analysis

Responses categorized as "yes" or "no" were considered to be an evaluable response to the questions; responses categorized as "don't know" or left blank were considered to be indeterminate and excluded from data analysis. All evaluable responses were coded and entered into a statistical database (MiniTab, version 11.0, MiniTab, Inc., State Park, PA). The frequency of positive or negative responses to individual questions constituted a conservative estimate of prevalence based on the total number of survey responses.

Descriptive statistics were applied to characterize the age groups, *MECP2* status, and height-, weight-, and BMI-for-age z-scores of the females with RTT. One-way analysis of variance was used to detect differences in height-, weight-, and BMI-for-age z-scores across the age groups of the RTT cohort. General linear modeling was applied to detect differences in height-, weight-, and BMI-for-age z-scores between females with and without *MECP2* mutations when adjusted for age. One- and two-sample t-tests were applied to determine

differences in height-, weight-, and BMI-for-age z-scores between the RTT cohort and the reference standard and between females with and without *MECP2* mutations, respectively.

Descriptive statistics were applied to determine the prevalence of gastrointestinal and nutritional problems in terms of clinical symptoms and diagnoses, diagnostic procedures, and medical, nutritional, and surgical interventions in the RTT cohort. The classification of clinical problems was based on groups of, as well as individual, symptoms and diagnoses as follows: 1) gastrointestinal dysmotility, including gastroesophageal reflux, gastroparesis, vomiting or regurgitation, nighttime awakening with irritability, constipation, straining with bowel movements, passage of hard stools; 2) feeding problems, including chewing difficulty, swallowing dysfunction, prolonged feeding time (> 30 min), choking or gagging with meals; 3) nutritional problems, including underweight, defined as BMI-for-age less than the fifth percentile, and overweight, defined as BMI-for-age greater than the eighty-fifth percentile (12); 4) short stature, defined as height z-scores < -2 SD of the reference standard (12); 5) skeletal abnormalities, including low bone mineral content (BMC) and fractures; 6) biliary tract disorders, including cholelithiasis and biliary dyskinesia, and 7) seizures. Diagnostic procedures included videofluoroscopic swallow function, upper gastrointestinal series, upper endoscopy, gastric emptying scan, abdominal ultrasound, colonoscopy, and bone density scan. Medical interventions included H_2-receptor and proton pump inhibitors, prokinetic medications, laxatives, and anticonvulsants. Nutrition interventions included the use of commercial formulas as primary or supplemental food sources, the ketogenic diet, and multivitamin and mineral or herbal supplements. Surgical interventions included fundoplication, gastrostomy, cholecystectomy, general abdominal surgery, and vagal nerve stimulator placement. Binary logistic regression was used to determine differences in the frequency of clinical symptoms and diagnoses, diagnostic tests, and medical, nutritional, and surgical treatments between females with and without *MECP2* mutations when adjusted for age group within the RTT cohort.

RESULTS

Demographics

The parental response rate to the questionnaire was 59% (n=983). The age distribution of the RTT cohort was: 0–5 y, 12%; 6–10 y, 22%; 11–14 y, 12%; 15–19 y, 17%; 20–29 y, 24%; and 30^+ y, 13%. MECP2 mutational analysis was performed in 659 (67%) and a mutation was found in 573 (87%).

The mean height-, weight-, and BMI-for-age z-scores for each age group with RTT decreased significantly with advancing age and were significantly lower than the reference standard (Table 1). The mean height- (-1.9 ± 2.2 vs. -1.6 ± 1.8, $P<0.001$) and weight- (-2.1 ± 3.0 vs. -1.8 ± 2.3, $P<0.001$), but not BMI- for-age (-0.9 ± 2.3 vs. -1.0 ± 1.8), z-scores were significantly lower in females with *MECP2* mutations than those without, respectively. Parental perceptions of underweight, normal weight, and overweight were associated ($P<0.001$) with calculated BMI-for-age z-scores.

Prevalence of Symptoms, Diagnoses, Procedures, Interventions

Symptoms and diagnoses associated with gastrointestinal dysmotility and feeding difficulties were reported to occur in the majority of the Rett cohort (Table 2), whereas a number of other gastrointestinal and nutritional symptoms were reported in some individuals. Straining with bowel movements, passage of hard stools, or constipation and prolonged feeding time or chewing difficulty were reported in more than one-half of the RTT cohort, whereas biliary tract disease, including cholelithiasis and biliary dyskinesia, occurred in only a small number of affected individuals.

Of the diagnostic procedures performed for gastrointestinal and nutritional problems, videofluoroscopic swallow function studies and upper gastrointestinal series were most commonly reported, but were performed only in approximately one-third of the RTT cohort (Table 3).

Laxatives were the medications most commonly used in nearly one-half of the RTT cohort. Commercial formulas and multivitamin and mineral supplements were the nutrition therapies most commonly used in approximately one-half of affected individuals. Gastrostomy placement was the surgical intervention most frequently performed in approximately one-fourth of the group.

Age Effect on Symptoms, Diagnoses

To assess the effect of age on the presentation of various symptoms or diagnoses, we calculated the odds ratio of having these features by age (Table 4). Features such as vomiting or regurgitation, nighttime awakening with irritability, gastroesophageal reflux, chewing difficulty, and choking or gagging with feeding were significantly less likely to occur in older than in younger individuals. In contrast, short stature, low BMC, fractures, and gastrostomy placement were significantly more likely to be presenting in older than in younger females with RTT. Underweight, overweight, prolonged feeding time, swallowing difficulty, gastroparesis, straining with bowel movements, passage of hard stool, constipation, cholelithiasis, or biliary dyskinesia, did not differ with age in RTT.

Mutation Effect on Symptoms, Diagnoses

Females with a *MECP2* mutation were less likely to have chewing difficulty [OR 0.47, $p<0.01$ (n=650)], choking or gagging with feeding [OR 0.52, $P<0.01$ (n=657)], or nighttime awakening with irritability [OR 0.29, $p<0.001$ (n=660)] than those without a *MECP2* mutation. Females with a *MECP2* mutation were more likely to have short stature [OR 2.17, $P<0.01$ (n=555)] than those without a *MEPC2* mutation. Underweight, overweight, vomiting or regurgitation, gastroesophageal reflux, gastroparesis, prolonged feeding time, swallowing difficulty, straining with bowel movements, passage of hard stool, constipation, low BMC, fractures, cholelithiasis, biliary dyskinesia, or gastrostomy placement did not differ between females with or without a *MECP2* mutation.

DISCUSSION

Although cognitive disabilities and seizures comprise overarching concerns, we found that gastrointestinal and nutritional problems occurred frequently throughout life in girls and women with RTT. In the present study, the majority of parents of a large RTT cohort reported one or more symptoms or diagnoses associated with gastrointestinal dysmotility and feeding difficulties in their affected daughters. Gastroesophageal symptoms and diagnoses were less likely to persist, whereas short stature and attention to bone health and alternative feeding methods were more likely to be present, with advanced age. Diagnostic evaluations and therapeutic interventions were utilized less frequently than the occurrence of reported symptoms or diagnoses. Increased physician and health care provider awareness of the gastrointestinal and nutritional manifestations of RTT, as well as the changing course of these problems as affected individuals grow older, may reduce the burden of care and improve the quality of life of girls and women affected with this disorder.

The gastrointestinal manifestations of RTT in the present study were protean and mirrored those reported by parents of children with other neurodevelopmental conditions such as autism spectrum disorders (ASD) (13,14). However, the prevalence of lower gastrointestinal symptoms such as constipation was two to nine fold more frequent and upper

gastrointestinal symptoms were 1.2 to 2.5 times more frequent in the RTT cohort than in children with ASD (13,14). As in ASD, gastroesophageal reflux and biliary tract disease may present with non-gastrointestinal symptoms such as nighttime awakening and unexplained irritability (14).

Feeding problems were reported frequently in the present study, although the prevalence varies across studies (7,8,15). Parents describe their daughters as having excellent appetites, but girls and women with RTT have greater difficulty eating solid foods than drinking thickened liquids because chewing difficulty prevails over swallowing dysfunction (8,15,16). Bruxism, involuntary tongue movements, and ineffective mastication, contribute to prolonged feeding time (17,18). Hypersalivation and hyperventilation may interfere with eating (16–18). Videofluoroscopy demonstrates universal delay in time between spoon feeding and swallowing solid food because of oropharyngeal dysfunction (7,18,19). The correlation between the delay in time to first swallow and advancing age implies a gradual deterioration of oromotor function, although parental perception in the present study did not corroborate this finding (18,20).

Short stature and altered body composition characterize the natural history of growth disturbances in RTT (3,6). In the present study, the pattern of height-for-age and weight-for-height deficits was consistent with that previously reported (3,8). A small proportion demonstrated weight-for-height excess, similar to the prevalence of overweight in children with ASD (14). Weight deficits in RTT have been attributed to alterations in energy balance (21). In the present study, supplemental formula use and a feeding gastrostomy supported the nutritional needs of these individuals, presumably preventing a decline in their BMI-for-age (22). Although undernutrition may be causally related to linear growth deficits, the difference in height z-scores between individuals with and without *MECP2* mutations in the present study underscores a genetic basis, in part, for growth failure in RTT (22).

Altered bone health, characterized as reduced bone mass, bone mineral deficits, and increased fracture rate, typifies RTT across a broad spectrum of *MECP2* mutations (6,24–29). The prevalence of low BMC and bone mineral density (BMD) reported in previous studies is higher than that found in the present study, presumably because of infrequent testing outside the research setting. Altered bone health is of concern because low BMD is associated with increased fracture risk in RTT (6,24,29). The prevalence of fractures in the present study is similar to that observed in most other RTT cohorts (6,24,25,29–31) and is estimated to be three to four fold higher than in healthy children (6,30,31).

Despite the increased prevalence of gastrointestinal and nutritional complaints, diagnostic procedures were performed less often and medications and nutrition supplements were administered less frequently than the occurrence of symptoms or diagnoses. Videofluoroscopic swallow function studies were performed in only 48% of individuals with feeding difficulties and upper gastrointestinal series, upper endoscopy, and gastric emptying scans were obtained in 59% to 79% of individuals reported to have gastroesophageal diagnoses. We previously documented that the scope and severity of some gastrointestinal problems may become apparent only when diagnostic studies are performed (7). In contrast, the seven fold increase in abdominal ultrasounds reflects early screening for unexplained irritability or apparent abdominal pain because of reported adverse outcomes when the diagnosis of cholelithiasis is delayed. We estimated that proton pump inhibitors, prokinetic medications, and laxatives were used by only 56%, 21%, and 59% of individuals affected with gastroesophageal reflux, gastroparesis, or constipation, respectively, and formulas and multivitamins were administered to 59% and 68%, respectively, of individuals affected with oropharyngeal dysfunction. Whether the use of medications and nutrition supplements was not attempted or was ineffective and abandoned is unknown.

Physician visits represent the largest component of health care use for most clinical conditions. Gastroesophageal reflux and functional bowel disorders comprise the highest number of physician visits annually in the ambulatory care setting and two of the five diagnoses with the largest outpatient physician charges (32,33). Proton pump inhibitors represent 77% of total cost for medications in the United States (32,33). The burden of gastrointestinal disease on the quality of life of patients is substantial, with functional disorders such as reflux and irritable bowel imposing a high level of disruption to individuals' lives (34). Although we did not provide a formal estimate, we assume that the physical, psychological, and economic burden of gastrointestinal disease in RTT is substantial based on the type and magnitude of gastrointestinal symptoms and diagnoses reported.

The limitations of our study included a partial response rate of 59% which may result in selection bias, as well as the absence of an unaffected control group with which to compare prevalence, duration, and severity of symptoms. We were unable to perform phenotype-genotype comparisons because specific RTT mutations were not obtained. The natural history study of RTT currently in progress will afford this opportunity in the future. In addition, the symptoms and diagnoses that we reported were based on parental perceptions rather than direct physician evaluation or review of medical records. Nevertheless, we found good agreement between parental perception of nutritional status and estimates of BMI, an observation that supports the reliability of parental reporting. Our list of symptoms and diagnoses was not all-inclusive in that complaints such as aerophagia and abdominal distention pose significant management issues in some individuals with RTT (35). Aerophagia, in conjunction with abnormal breathing patterns (36), contributes to gastric dilatation and perforation (9,10,37), findings that may be causally related to morbidity and mortality in individuals with mental and physical disabilities (38,39). In our experience, gastric and intestinal perforations in females with RTT have been found alone or in conjunction with volvulus and intussusception. These entities concern us because they may occur more frequently and with fewer signs and symptoms in cognitively impaired individuals, particularly in the setting of chronic constipation and megacolon (40).

CONCLUSION

Gastrointestinal and nutritional problems occur frequently throughout life in females with RTT and pose a significant medical burden to their caregivers. Physician and health care professional awareness of these problems may improve the health and quality of life of females affected with RTT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources

Funding for this project was provided by the International Rett Syndrome Foundation, the Rett Syndrome Association of Illinois, The Blue Bird Circle, and the National Institutes of Health (NICHD U54 HD061222, NCRR U54 RR019478, and the Office of Rare Diseases Research). The views expressed in written materials or publications do not necessarily reflect the official policies of the Department of Health and Human Services, nor does mention by trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

This work is a publication of the USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX, and has been funded in part with federal funds from the US Department of Agriculture, Agricultural Research Service (Cooperative Agreement Number 58-6250-1-003). The content of this publication does not

necessarily reflect the views or policies of the US Department of Agriculture, nor does mention of trade names commercial products, or organizations imply endorsement by this agency.

The authors thank the administrative staff of the IRSF for their support in processing the survey forms, the families of girls and women with RTT for their participation in completing the survey, J. Kennard Fraley for providing z-score values, E. O'Brien Smith, Ph.D. for statistical consultation, Jeffrey P. Kirsches, Ph.D., Professor and Division Chief, Data and Technology Coordinating Center, University of South Florida, for providing data analysis support, and Mary Lou Oster-Granite, Ph.D., who provided invaluable guidance, support, and encouragement for this Rare Disease initiative.

Abbreviations

ASD	autism spectrum disorders
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
IRSF	International Rett Syndrome Foundation
MECP2	methyl-CpG-binding protein 2
NCRR	National Center for Research Resources
NIH	National Institutes of Health
RDCRN	Rare Disease Clinical Research Network
RTT	Rett syndrome

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J Pediatr Gastroenterol Nutr. Author manuscript; available in PMC 2013 September 01.

Table 1

Height-, weight-, and BMI-for-age z-scores for each age group of girls and women with Rett Syndrome (n=983)[1]

Age Group (y)	N	Height-for-age (z-score)	N	Weight-for-age (z-score)	N	BMI-for-age (z-score)
0–5	90	−0.6 ± 2.5*	111	−0.8 ± 2.2*	90	−0.5 ± 2.3*
6–10	173	−1.6 ± 2.2	217	−1.3 ± 2.1	173	−0.5 ± 2.1
11–14	91	−2.1 ± 1.6	112	−1.9 ± 2.0	91	−0.9 ± 1.9
15–19	153	−2.7 ± 2.0	168	−3.5 ± 3.6	152	−1.2 ± 2.3
20–29	216	−2.7 ± 1.6	234	−3.6 ± 3.2	215	−1.5 ± 2.2
30–40+	121	−2.5 ± 1.9	123	−3.1 ± 3.1	121	−1.3 ± 2.5
0–40+	844	−2.2 ± 2.1**	965	−2.5 ± 3.0**	842	−1.0 ± 2.3**

[1] Data expressed as absolute values and z-scores (mean ± SD)

* P<0.001, difference among age groups across time

** P <0.001, difference between Rett syndrome cohort and reference standard (11)

Table 2

Prevalence of gastrointestinal and nutritional symptoms and diagnoses reported by parents (n=983) of girls and women with Rett syndrome on a structured survey questionnaire

Diagnosis or Symptom	Proportion of Cohort (%)
Feeding problems	**81**
Chewing difficulty	56
Prolonged feeding time (30–60 min)	62
Swallowing difficulty	43
Choking/gagging with feedings	27
Gastrointestinal problems	**92**
Gastroesophageal reflux	39
Vomiting or regurgitation	10
Nighttime awakening with irritability	16
Gastroparesis	14
Constipation	80
Straining with bowel movements	69
Passage of hard stools	61
Biliary tract disorders	**3**
Cholelithiasis	2
Biliary dyskinesia	1
Nutritional problems	**47**
Poor weight gain, underweight	38
Overweight	9
Short stature	**45**
Skeletal problems	**37**
Low bone mineral content	17
Bone fracture	30
Seizures	**81**
Presently symptomatic	52

Table 3

Frequency of procedures and medical, nutritional, or surgical interventions reported by parents (n=983) of girls and women with Rett syndrome on a structured survey questionnaire

Intervention	Proportion of Cohort (%)
Procedures	
Videofluoroscopic swallow function	39
Upper gastrointestinal series	30
Upper endoscopy	23
Gastric emptying scan	11
Abdominal ultrasound	20
Colonoscopy	6
Bone density scan	19
Medical *	
H_2-receptor inhibitors	7
Proton pump inhibitors	22
Prokinetics	3
Laxatives	47
Anticonvulsants	68
Nutritional	
Commercial formulas	48
Primary food source	16
Supplemental food source	32
Ketogenic diet	7
Multivitamin/mineral supplement	55
Herbal supplement	19
Surgical	
Fundoplication	11
Gastrostomy	28
Cholecystectomy	3
General abdominal surgery	5
Vagal nerve stimulator placement	5

* Medical therapies, including H_2-receptors, proton pump inhibitors, prokinetics, and laxatives, derived from the Rate Disease Clinical Research Network for Rett syndrome database (n=647)

Table 4

Odds ratios of age-related occurrence of symptoms or diagnoses and nutritional or surgical interventions reported by the parents (n=983) of girls and women with Rett syndrome

Variable	Number	Age group (y)	P-value	Odds Ratio*
Vomiting or regurgitation	656	6–10	ns	--
		11–14	ns	--
		15–19	0.01	0.24
		20–29	0.01	0.27
		30–40+	0.06	0.30
Nighttime awakening with irritability	660	6–10	ns	--
		11–14	0.03	0.43
		15–19	0.01	0.36
		20–29	0.01	0.32
		30–40+	ns	--
Gastroesophageal reflux	571	6–10	ns	--
		11–14	0.01	0.39
		15–19	0.01	0.46
		20–29	0.05	0.56
		30–40+	ns	--
Chewing difficulty	650	6–10	ns	--
		11–14	ns	--
		15–19	0.01	0.48
		20–29	0.01	0.42
		30–40+	ns	--
Choking or gagging with feeding	657	6–10	0.01	0.54
		11–14	0.001	0.31
		15–19	0.001	0.31
		20–29	0.02	0.51
		30–40+	0.001	0.15
Short stature	555	6–10	ns	--
		11–14	0.001	3.10
		15–19	0.001	4.74
		20–29	0.001	5.76
		30–40+	0.001	5.96
Low bone mineral content	377	6–10	0.01	15.4
		11–14	0.001	30.4
		15–19	0.001	36.3
		20–29	0.001	67.5
		30–40+	0.001	140.3
Bone fracture	647	6–10	0.001	4.28
		11–14	0.001	5.83
		15–19	0.001	7.05

Variable	Number	Age group (y)	P-value	Odds Ratio*
		20–29	0.001	10.95
		30–40+	0.001	13.06
Seizures currently	623	6–10	0.001	2.41
		11–14	0.001	3.63
		15–19	0.001	2.98
		20–29	0.04	1.85
		30–40+	ns	--
Gastrostomy placement	658	6–10	0.001	2.96
		11–14	0.001	5.14
		15–19	0.001	5.14
		20–29	0.001	3.24
		30–40+	ns	--

*Odds Ratio for each age group relative to the youngest age group, 0–5 y