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Feeding Experiences and Growth Status in a Rett Syndrome Population

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ABSTRACT

Objectives: Feeding difficulties in Rett syndrome are complex and multifactorial. In this study, we describe the feeding experiences in Rett syndrome and examine the factors affecting growth.

Materials and Methods: Using questionnaire data related to a population-based cohort, ages 2 to 29 years (n = 201), we measured the feeding experiences, growth, and factors affecting growth (enteral nutritional support, mutations, mobility, breath-holding, hyperventiliation) in subjects with Rett syndrome.

Results: The mean weight, height, and body mass index *z* scores in subjects with Rett syndrome were below that of their age group and decreased steadily with age. Twenty percent of subjects had enteral nutrition support, and it was more common in the older age group. Those with truncating mutations had significantly less enteral nutrition support than the other mutation groups. Furthermore, those with low mobility had lower mean body mass index *z* scores than those with higher mobility, and increased frequency of breath-holding and hyperventilation also was associated with lower body mass index *z* scores.

Conclusions: Routine monitoring of growth should continue to determine the severity of nutritional problems in Rett syndrome. Active nutritional management is recommended to ensure females affected with Rett syndrome have the best opportunity to reach their growth potential. ***JPGN 45:582–590, 2007.*** **Key Words:** Enteral nutrition support—Feeding difficulties—Growth—Nutritional status—Rett syndrome.

INTRODUCTION

Rett syndrome is a severe neurodevelopmental disorder affecting predominately females, and usually caused by mutations in the *MECP2* gene on the X chromosome (1). It is characterised by the loss of fine and gross motor skills and communication ability, slowing of head growth, and the development of stereotypic hand movements, following a period of generally normal development (2). Females with Rett syndrome also commonly develop seizures, breathing disturbances, scoliosis, growth retardation, and gait apraxia. Somatic growth failure also is a major aspect of the developmental arrest (3,4).

The feeding difficulties in Rett syndrome have not been as well described as they have, for instance, in cerebral palsy; however, Rett syndrome often is associated with impairment of self-feeding, nutritional intake, and growth (5). In a study involving a chart review of 22 girls with Rett syndrome and a similar number with a range of other developmental disabilities, those with Rett syndrome had significantly lower body weights; more respiratory, gastrointestinal, and swallowing difficulties; less self-feeding ability, and lower texture tolerance for chewy and crunchy foods (6). Rett syndrome is notable for a decline in feeding ability that may occur without warning with increasing age. Vigilance for such a decline and resultant nutritional compromise may help prevent the emergence of comorbidities associated with nutritional inadequacy.

Feeding difficulties in neurological conditions are complex and involve oromotor, behavioural, nutritional, and medical components (7). Oromotor problems may include oropharyngeal dysfunction, sensory deficits,

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reduced tongue mobility, and texture intolerance (8,9). One or all of the phases of swallowing may be involved, and oral, pharyngeal, and oesophageal factors may be difficult to distinguish. For example, reduced muscle tone affecting muscles of the head and neck may be 1 factor in reduced tolerance to textures; breathing disturbances may interfere with swallowing ability; presence of seizures may require medication that affects appetite, causes sedation, or increases oral secretions; and unmanaged constipation also may affect appetite (10). As a result of the severe feeding difficulties seen in Rett syndrome, enteral nutritional support (ENS), which is generally used to improve nutritional status (11), is often initiated (12). ENS through percutaneous endoscopic gastrostomy (PEG) feeding is useful for longer-term feeding (13), whereas nasogastric tube feeds are the preferred route of administration for short-term use.

The aims of this study were to describe the feeding difficulties and nutritional status of a population-based cohort of 201 subjects with Rett syndrome ages 2 to 29 years and to examine the relationship between anthropometric measures—including weight, height, and body mass index (BMI) for age z scores—and age, enteral nutritional support, genetic mutations, feeding difficulties, and other clinical features. The Ethics Committee of the Women's and Children's Health Services in Western Australia approved the study.

MATERIALS AND METHODS

The Australian Rett Syndrome Database is an ongoing population-based register of Rett syndrome cases born since 1976 (14). Cases are located through multiple sources, principally the Australian Paediatric Surveillance Unit and the parent support group, the Rett Syndrome Association of Australia. At enrollment, questionnaires are completed by the family and by the child's managing clinician. The register was established in 1993, and by the end of 2004, 9.1% (n = 24) of cases in the cohort had died, such that survival was 77.8% at the age of 25 years (15).

Since 2000, follow-up questionnaires have been administered to the families or other caregivers every 2 years (14,16). Data collected includes information on the individual's height and weight (or supine length if unable to stand), functional ability in daily living, behaviour, hand function, medical conditions, and use of health and education services. The mealtime component of the questionnaire, administered in 2004, covered feeding difficulties, special food preparation, signs of oromotor dysfunction, enteral nutritional support, and other types of supplementary feeding. Data used in this analysis were responses to the 2004 questionnaire, which was returned by 97% (201/217) of study families to whom it was administered. The age of the Rett syndrome subjects varied from 2 to 29 years (mean 15 years). Age groups were categorized as follows: <7 years old (generally equivalent to younger than school age), 7 to <12 years old (relating to primary-school age), 12 to <17 years old (equivalent to secondary school), and ≥17 years (relating to adult women). The age cutpoints were broadly based on a previous analysis by this research group (14).

Feeding Experiences

Feeding experiences were ascertained from a series of items in the 2004 questionnaire and addressed the domains of feeding method, food textures, mealtime behaviours, and average intake of food and liquid. Feeding method was recorded as oral or enteral feeds. ENS was recorded as no ENS, a gastrostomy button, or a nasogastric tube, and the latter 2 responses were combined for any ENS. Questions were asked about special food-preparation requirements (eg, bite-sized, mashed, pureed), details of specific foods that were difficult to eat, and use of thickening agents. Mealtime behaviours were recorded as coughing, choking, or gagging with various food textures. Mealtime practices were recorded as routines at meal times, average length of meal times, and whether special utensils were required for drinking and eating. Average intake of food was estimated by the parent (or caregiver), who was asked if the quantity of food that their daughter ate was about right, less than, or more than expected for someone of her size. Parents or caregivers also were asked to estimate the average liquid intake in cups per day, and to document their degree of concern about the adequacy of fluid intake. Feeding difficulties were classified as none, mild, moderate, or severe using the classification system developed by Morton et al (17) and based on duration of meal time and need for mashed food. Mild feeding difficulties were defined as solids need to be mashed or pureed but average duration of meal <15 minutes, moderate feeding difficulties were defined as average duration of meal 15 to 30 minutes, and severe feeding difficulties were defined as average duration of meal >30 minutes.

Growth Indices

In the absence of specific nutritional intake data, measures of growth (height and weight) were used to determine the severity of nutritional problems. Information on weight was available in 166 of 201 unique cases, on height in 156 of 201 unique cases, which enabled the calculation of a BMI score in 151 of 201 (75%) unique cases. Height, weight, and BMI z scores for age were calculated using the US Centers for Disease Control and Prevention (18) online data files. These contain the median (M), generalised coefficient of variance (S), and power in the Box-Cox transformations (L) for weight, height, and BMI listed in age at half-months for boys and girls (19). These data were used to calculate the z scores (Z) for weight, height, and BMI as

$$Z = \frac{\left[\frac{X}{M}\right]^{L} - 1}{LS}$$

where X represents the measurement of the individual at a specific age. The age in months for cases in our cohort was calculated by subtracting the date of birth from the date on which the measurement was taken and rounding to the nearest half-month to map to the CDC charts. The reference value for age 20 years was also applied to any individual over this age. The z score for head circumference (HC) in 2000 was calculated based on the following formula: (HC of child − reference mean HC)/reference standard deviation (SD) of HC. The reference mean and SD were obtained from a Dutch study that provided population norms (20).

Comorbidities (With Potential for Impact on Growth)

Parents or caregivers were asked whether the subject had been diagnosed with scoliosis, epilepsy, or constipation, or if breathing difficulties or hyperventilation had been observed, as well as the extent of the subject's mobility. For the last 3 measures, items from the Rett Syndrome Symptom Index Score were used. This index, which was designed to predict and measure clinical severity in Rett syndrome, uses a 16-item assessment tool, with each item individually rated from 0 to 8, with 8 being the best possible score and 0 the worst (21). Parents or caregivers also were asked to indicate the frequency of breath-holding (coded using a 9-point scale, from constantly holding her breath to never holding breath) and of hyperventilation, which was coded in a similar fashion. The mobility question asked the parent or caregiver to rate their daughter's mobility on a 9-point scale from wheelchair-bound (0), crawling (2), walking with assistance (4), unsteady walking (6), through walking unaided (8). For the purposes of this study, the mobility scale was recoded to low-mobility ''Wheelchair Bound to Crawling/Supported Walking'' (codes 0–4) and high-mobility ''Unsteady Walking to Walking Unaided'' (codes 5–8) to separate those who were independently ambulatory from those who were not.

Genetic Status

In 2000 all of the families participating in the study were offered the opportunity to have their child tested for *MECP2* mutations (22). These genetic results and those of subsequently enrolled and tested individuals have been included. Genetic information was initially categorised by the following mutation grouping: absence of mutation, early truncating, late truncating, large deletions involving exon 3 and 4, and missense mutations (mutation grouping 1). In a second grouping (mutation grouping 2), the common mutations p.R168X, p.T158M, p.R294X, p.R270X, p.R255X, p.R133C, and p.R306C were included as separate entities.

Statistical Methods

Significance tests for contingency tables were based upon the chi-square test for association (without continuity correction) and used for comparing categorical variables. Student *t* tests were applied to determine mean differences for continuous variables for 2 groups and analysis of variance for groups with more than 2 levels. Statistical significance was defined at the 2-sided $P = 0.05$ level. The Pearson correlation statistic was used to investigate the relationship between 2 continuous variables, as was linear regression where appropriate. Data were analysed using STATA version 9 (23) and the Statistical Package for Social Sciences, version 11.5 (24).

RESULTS

The mean age of the subjects with Rett syndrome was 15.24 years with a range of 2.33 to 29.10 years (Table 1). Eighty-three percent (167/201) had been diagnosed with

TABLE 1. *Characteristics of cohort by age group*

Characteristic	Total	Age group, y			
		0 to <7	7 to <12	12 to <17	≥17
Average age, y	15.24	4.93	9.21	14.36	21.98
No. of cases, n (%)	201 (100)	27 (13.4)	43 (21.4)	46 (22.9)	85 (42.3)
Total group (n = 201)					
Average weight, kg	33.36	18.05	25.42	36.68	42.05
Average height, cm	134.14	103.95	123.33	141.53	146.23
Mean BMI	18.26	16.30	16.37	18.11	20.00
Presence of enteral nutritional support (%)	40/201 (19.9)	3/27 (11.1)	10/43 (23.3)	11/46 (23.9)	16/85 (18.8)
Diagnosis of epilepsy (%)	165/199 (82.9)	14/26 (53.9)	32/43 (74.4)	41/46 (89.1)	78/84 (92.9)
Scoliosis (%)	120/143 (83.9)	6/8 (75.0)	25/31 (80.6)	29/33 (87.9)	60/71 (84.5)
Breathing difficulties (%)	129/196 (65.8)	16/27 (59.3)	28/43 (65.1)	27/43 (62.8)	58/83 (70.0)
Constipation (%)	122/201 (60.7)	9/27 (33.3)	15/43 (34.9)	16/46 (34.8)	39/85 (45.9)
Poor mobility (unable to walk or only with assistance) (%)	119/195 (61.0)	11/27 (40.7)	15/42 (35.7)	20/43 (46.5)	30/83 (42.6)
Difficulty with or not able to eat any particular food (%)	119/184 (64.7)	17/26 (65.4)	30/39 (76.9)	24/42 (57.1)	48/77 (62.3)
Chokes, gags, or coughs on liquids, solids, or purees > once per day (%)	56/201 (27.9)	11/27 (40.7)	15/43 (34.9)	12/46 (26.1)	18/85 (21.2)
Genetic characteristics					
Absence of mutation (%)	41/201 (20.4)	2/27 (7.4)	10/43 (23.3)	14/46 (30.4)	15/85 (17.7)
Early truncating (%)	53/201 (26.4)	8/27 (29.6)	10/43 (23.3)	12/46 (26.1)	23/85 (27.1)
Late truncating (%)	33/201 (16.4)	4/27 (14.8)	8/43 (18.6)	6/46 (13.0)	15/85 (17.7)
Large deletions (%)	10/201 (5.0)	3/27 (11.1)	1/43 (2.3)	4/46 (8.7)	2/85 (2.4)
Missense (%)	52/201 (25.9)	8/27 (29.6)	11/43 (25.6)	9/46 (19.6)	24/85 (28.2)
Exon 1 (%)	1/201 (0.5)	0/27 (0)	0/43 (0)	1/46 (2.2)	0/85 (0)
Not tested (%)	11/201 (5.5)	2/27 (7.4)	3/43 (6.98)	0/46 (0)	6/85 (7.1)

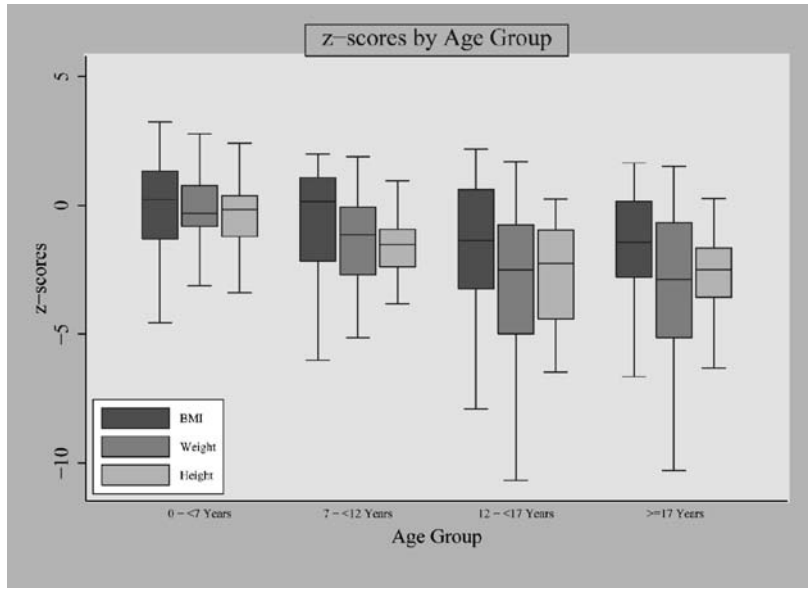

FIG. 1. Weight, height, and BMI-for-age *z* scores by age group (all subjects).

epilepsy, and prevalence increased with age group, as did breathing difficulties and scoliosis as reported by parents. The mean weight of the subjects varied from 18 kg in those under 7 years to 42 kg in those 17 years and over, mean height varied from 104 cm to 146 cm, and mean BMI from 16.3 to 20.0 (Table 1). Mean weight, height, and BMI for age *z* scores of Rett syndrome subjects were below that of their age group, as demonstrated by the negative *z* scores (Fig. 1), but 3.0% (5/161) had a BMI *z* score greater than 2. They also decreased progressively with age, with the following regression coefficients and confidence intervals: −0.068 (CI −0.128 to −0.008) for BMI *z* scores, −0.145 (CI −0.205 to −0.085) for weight *z* scores, and −0.095 (CI −0.134 to −0.056) for height *z* scores.

Feeding Experiences

Enteral Nutrition Support

One-fifth of the subjects (40/201) had ENS, with the age group having the highest proportion of ENS being the 12- to 17-year-olds (23.9%) and the lowest the 0- to 7-year-olds (11.1%). Most parents of those not on ENS, when asked if their daughter ''ate less,'' ''about right,'' or ''more than expected,'' thought their daughter ate the right amount (Table 2); however, when asked about their daughter's liquid intake, 34.4% either frequently or constantly worried that their daughter did not consume enough liquid. ENS reduced this concern, although 43% of parents still had some concerns about fluid intake.

TABLE 2. *Information about meal times from parental perspective (cases without enteral nutritional support, n = 161)*

	Age group				
	0 to <7	7 to <12	12 to <17	≥17	All
No. of cases	24	33	35	69	161
Parental concern about food quantity, %					
Less than expected	25.0	30.3	24.2	11.8	20.3
About right	45.8	33.3	42.4	64.7	50.6
More than expected	29.2	36.4	33.3	23.5	29.1
All	100.0	100.0	100.0	100.0	100.0
Parental concern about liquid intake, %					
No worries	16.7	12.1	40.0	36.8	29.4
Occasional worries	41.7	33.3	28.6	39.7	36.3
Frequently worries	12.5	33.3	14.3	16.2	18.8
Constantly worries	29.2	21.2	17.1	7.4	15.6
All	100.0	100.0	100.0	100.0	100.0
Mean length of meal time, min	23.54	27.42	22.57	24.21	24.43
Estimated average liquid intake, cups/d	2.84	3.22	4.98	5.08	4.35

Feeding Difficulties

The mean duration of meal times, on average, was 24.4 minutes. According to the classification used by Morton et al (17) and based on duration of meal time, 5 of 158 (3.2%) subjects without ENS would be classified as having mild, 115 (72.8%) moderate, and 23 (14.6%) severe feeding difficulties. Nearly two-thirds (61.5%) of families whose daughters were not on ENS stated that there were foods their daughter had difficulty eating or was not able to eat. A substantial proportion (60.2%) of those not on ENS needed their food to be pureed, mashed, or chopped, and only 11 (6.8%) did not require any special food preparation. Fifteen (9.3%) of those without ENS also had their liquids thickened using 1 of a number of prescribed commercially available proprietary thickeners. Only a small number (n = 10) (6.2%) of those only fed orally were reported to choke or gag on their food or drink daily or more. A slightly higher proportion coughed when drinking liquids (21.9%), eating purees (7.6%), eating solids (11.2%), or eating more than 1 texture at a time (9.8%). There was no evidence of an increase in these problems by age group. No relationship between feeding difficulty category and age group ($P = 0.61$) or type of genetic mutation ($P = 0.51$) was apparent.

Growth Indices and Associated Factors

Age

There were no significant differences in BMI, weight, or height z scores in any age group when those with and without ENS were compared. However, the subjects in the 17-and-older age group with ENS did have lower BMI z scores than their counterparts without ENS ($P = 0.07$), and the subjects with ENS also had lower height z scores than their counterparts without ENS ($P = 0.06$) in the 0- to 7-years-old group.

Feeding Time

There was no significant relationship between the average time taken to feed and the BMI, weight, or height z scores. However, if the longest time to feed was considered instead of the average time, there was an association with those who took longer to feed being significantly more likely to have more negative BMI z scores than those who took less time to feed ($\rho = -0.194$; $P = 0.021$).

Mobility

Those with lower mobility had lower mean BMI z scores than those with higher mobility at all ages except the 7- to 12-years-old group (Fig. 2). The pattern was similar for weight z scores, but the height z scores for those with lower mobility were lower for all age groups. Those with ENS also were significantly more likely ($P < 0.001$) to have lower mobility than those without ENS.

Reported Breathing Abnormalities, Epilepsy and Other Comorbidities

BMI z scores were significantly correlated with breath-holding ($\rho = 0.17$; $P = 0.044$) and hyperventilation ($\rho = 0.23$; $P = 0.005$) as were weight z scores for breath-holding ($\rho = 0.22$; $P = 0.006$) and hyperventilation

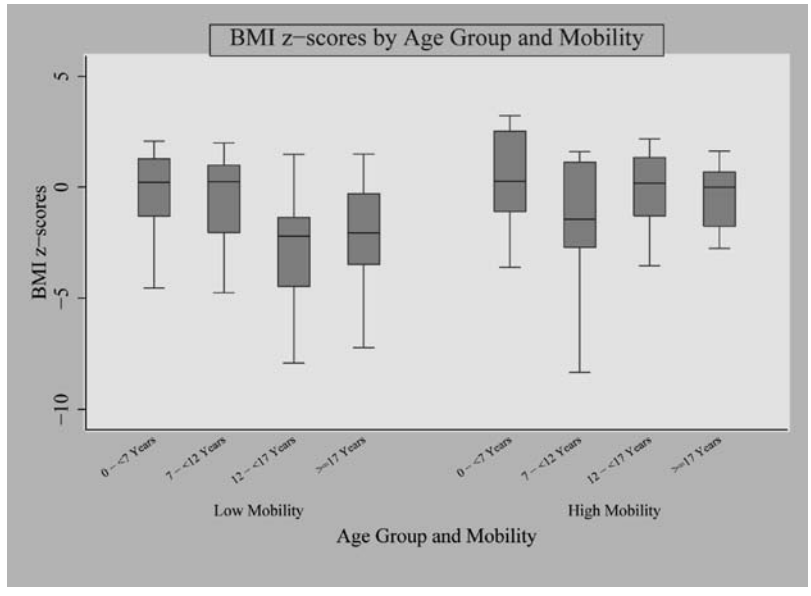

FIG. 2. BMI z scores by age group and mobility (all subjects).

($\rho = 0.21$; $P = 0.007$). A similar pattern was seen for height z scores for breath-holding ($\rho = 0.19$; $P = 0.02$) and hyperventilation ($\rho = 0.13$; $P = 0.10$). In each case, increased frequency of breath-holding and hyperventilation was associated with a lower z score. For those without ENS, the BMI z score was lower, but not significantly so for girls with breathing problems (mean -1.47) compared with those with no breathing problems (mean -0.68; $P = 0.13$); however, the weight z scores ($P = 0.02$) and height z scores ($P = 0.01$) were significantly lower for those with breathing problems. The weight ($P = 0.01$) and height ($P < 0.001$) but not the BMI z scores ($P = 0.09$) were significantly lower in those without ENS and with an epilepsy diagnosis. There was no statistically significant association between the z scores and presence of either constipation or scoliosis, or with the frequency of hand stereotypies in those without ENS. We also investigated the relationship between head-circumference z score and each of the BMI, weight, and height z scores and found that all 3 were significantly ($P < 0.001$) associated with current head-circumference growth.

Genetic Status

In those tested for mutations (n = 190), 18.4% had ENS. Although not significantly different, ENS was common in those with early truncating mutations (40%), p.R255X (36.4%), and p.T158M (31.3%), and less common in C-terminal deletions (5.6%) and p.R270X (7.7%). No subjects with p.R294X and p.R306C had ENS; however, late-truncating mutations as a group had significantly less ENS than other large mutation groups (3.3%; $P = 0.05$).

We examined BMI, weight, and height z scores by genetic profile for individuals without enteral support, but did not identify any overall statistically significant differences between groups. We found that those with late-truncating mutations had the highest BMI (significantly higher than those with large deletions) (Fig. 3A) and weight z scores (significantly higher than those with missense and early-truncating mutations). In the more specific grouping, C-terminal deletions had the highest z scores for weight and BMI. Their BMI z scores also were significantly higher when compared with all other mutations (0.58 vs -1.53; $P = 0.007$) (Fig. 3B). There was generally less variation for height z scores.

DISCUSSION

We found that mean weight, height, and BMI z scores for individuals in this Rett syndrome cohort were below that of their age group in the general population and decreased steadily with age. Twenty percent had ENS, and it was more common in the older age groups compared with the younger age groups. Those with late-truncating mutations had significantly less ENS than the other mutation groups. Furthermore, those with low mobility had lower mean BMI z scores compared with those with higher mobility, and those with breath-holding and hyperventilation had lower BMI z scores than those without these problems.

As has been reported elsewhere in a case series (25), females with Rett syndrome were generally small, with mean weight, height, and BMI for age z scores well below the population mean for age groups and profoundly so from 12 years of age. In the broader categorization of mutation type, those with late-truncating mutations had significantly higher BMI for age z scores than those with large deletions, and higher weight z scores than those with missense and early-truncating mutations when we excluded those who were on enteral support. When examining mutation groups more specifically, those with C-terminal mutations also were found to have higher BMI-for-age z scores. These mutations have been linked to a milder clinical profile at least when the patient is younger (26). When we examined the relationship between mutation type and being on ENS, we found that those with known milder mutations such as p.R294X (27,28) and p.R306C (29), as well as the C-terminal deletions, were less likely to be using ENS. There was also low ENS use for those with p.R270X, which we have previously characterized as a severe mutation (27,30), but this may be due to a survivor effect because we already have shown that this was the single mutation with the highest mortality in our cohort (30). Further research is required in larger populations to confirm these findings.

Lower BMI z scores for age were seen in those who were constantly hyperventilating and in those with lower mobility. Although abnormal breathing could be expected to interfere with eating and be associated with greater energy expenditure, those with low mobility may be expected to expend less energy. The lower BMI z scores for age in less mobile people suggest an association with other factors affecting energy balance. Isaacs et al (6) previously found that microcephaly was associated with lower weight-for-age z scores, and we found a similar relationship between head-circumference z scores and BMI, weight, and height z scores. This may indicate—as suggested by the relationships that we noted between ENS use and mutation type—that the growth potential for these subjects may be strongly influenced by genetic factors already determined by birth.

We know that there are multiple factors operating singly or in combination affecting energy balance that can potentially result in impaired growth, including inadequate dietary intake, malabsorption, altered metabolic processes, or increased metabolic rate (31). Motil and colleagues (32) reported in 1994 that metabolic rate in girls with Rett syndrome was lower while sleeping, but not while awake, than in healthy controls, and that involuntary motor movement took 2.4-fold more time compared with controls. These researchers found a negative energy balance, which they hypothesized could result in growth failure, if sustained over a number of

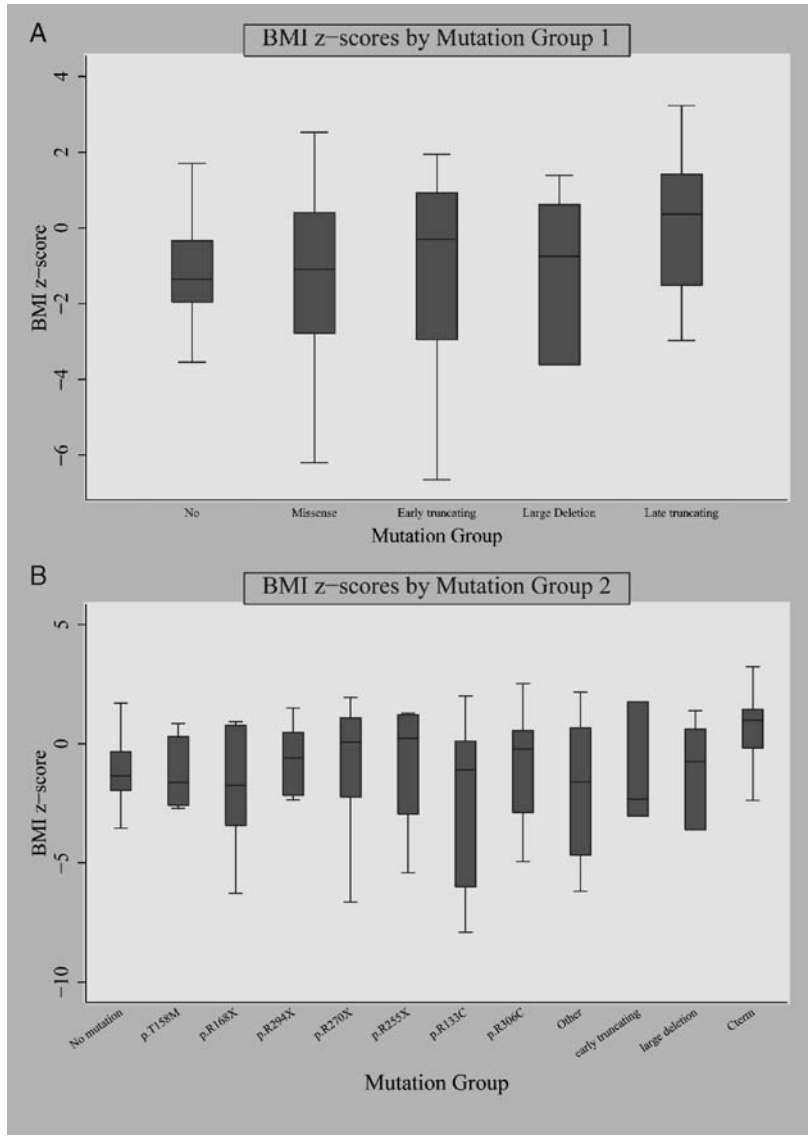

FIG. 3. A, BMI *z* scores by mutation group 1 (subjects with no enteral support). B, BMI *z* scores by mutation group 2 (subjects with no enteral support).

years. In a subsequent study, 4 years later, they further investigated whether such increased energy expenditure could be due to repetitive movements and muscle spasms (31). They found that the repetitive, involuntary movements did not increase total daily energy expenditure, which was lower than for healthy age-matched controls.

As seen in the reports of Budden (11,33,34), a large proportion of our cohort had some level of feeding difficulty and 60% of the group needed their food to be pureed, mashed, or chopped. The average meal time was 25 minutes with up to 2 hours being the longest time taken to complete a meal, with 87.4% having moderate to severe feeding difficulties using the Morton et al classification (17). Although there was no relationship between feeding difficulties and age or presence or absence of a mutation, those who took longer to feed had lower BMI *z* scores for age. Despite this, nearly one-third of those in our study were reported to eat more than expected and less than one-fourth (20.3%) less than expected. This contrasted with high concern about fluid intake. Motil et al (35), in an investigation of 13 cases, also found that parents reported that participants had ''good appetites,'' although intake of total energy and calcium was much lower than that of height- and age-matched reference values. Furthermore, parents with children with cerebral palsy have been shown to overreport food intake using weighed food records compared with measures of total energy expenditure (36).

Although only small numbers of our cohort were reported to choke, almost 25% had problems with coughing with liquid, suggesting poor laryngeal closure and indicative of swallowing problems and possible aspiration. Using video fluoroscopy to demonstrate aspiration, Morton et al (17) found that girls who were aspirating were more likely to be in the most severe range of symptoms, nonambulatory and the most growth retarded. It is possible that these problems are associated with the increasing rigidity that can occur with age. When studying the motor and behavioral findings in 32 Rett syndrome patients, Fitzgerald et al (37) found that the movement disorder tended to be more hyperkinetic in the younger and more bradykinetic in the older patients.

Previous studies have shown that the reasons for PEG insertion in Rett syndrome include severe gastro-oesophageal reflux (when combined with fundoplication), dysphagia, growth failure or profuse drooling, and an inability to close the mouth during swallowing (38). Twenty percent of the subjects in our study had a PEG. Gastrostomy feeding has been shown to be associated with weight and health gains in children with severe disability of varying aetiology (39). In individuals with cerebral palsy, it has been shown to result in weight gain and accelerated height growth thought to represent ''catch up'' following undernutrition (40).

PEG insertion also can improve quality of life, with caregivers reporting a significant reduction in feeding times, increased ease of medication administration, and reduced concern over the child's nutritional status (39,41). In our Rett syndrome study, there was no evidence of better growth indices in those with ENS. Because of the cross-sectional nature of the data, we did not have the capacity to examine the effects of a PEG on subsequent growth and nutritional status. Surprisingly, in our study there was continued concern about fluid intake after PEG insertion, and this and the lack of improvement in nutritional status require further investigation using longitudinal data.

A strength of our study is the large sample size and the representativeness of the Australian population with Rett syndrome. Because of the geographical size of Australia, we relied on parent-reported data for height and weight. As a result, there could be measurement and reporting error with variability between scales as well as interrater variability for height measures in particular, which may have been measured by tape. Although the measurements often were taken in clinical settings, even in clinical settings it is acknowledged that girls with Rett syndrome are difficult to measure. The cross-sectional nature of this study's data also could have an impact on the stabilization of growth status seen in the older age group, in which there may be a survivor bias, with those with greater clinical severity likely to have died. In future data analyses, we aim to use retrospective data to examine and investigate the factors affecting the trajectory of growth in Rett syndrome over time. A greater understanding of these factors and the best methods to monitor growth and nutritional status is essential to provide the best quality of life for girls and women with Rett syndrome and their caregivers.

Growth retardation in Rett syndrome is complex. The feeding difficulties have the potential to impact on adequate nutritional intake if effective intervention is not instituted, as well as putting considerable strain on parents and caregivers. Nutritional monitoring and advice as to food choices that match feeding abilities should be an integral part of the care in Rett syndrome. Routine monitoring of growth (height and weight) should continue to determine the severity of nutritional problems. It would appear, however, from the association of somatic growth with head growth and, because of the relationships we identified with some mutation groups, that genotype is likely to have an influence on growth. This study adds to our understanding of the multiple and interacting factors affecting growth in Rett syndrome.

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REFERENCES

1. Amir RE, Van den Veyver IB, Wan M, et al. Rett syndrome is caused by mutations in x-linked mecp2, encoding methyl-cpg-binding protein 2. *Nat Genet* 1999;23:185–8.
2. Hagberg B, Aicardi J, Dias K, et al. A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. *Ann Neurol* 1983;14:471–9.
3. Schultz R, Glaze D, Motil K, et al. Hand and foot growth failure in Rett syndrome. *J Child Neurol* 1998;13:71–4.
4. Schultz RJ, Glaze DG, Motil KJ, et al. The pattern of growth failure in Rett syndrome. *Am J Dis Child* 1993;147:633–7.
5. Reilly S, Cass H. Growth and nutrition in Rett syndrome. *Disabil Rehabil* 2001;23:118–28.
6. Isaacs JS, Murdock M, Lane J, et al. Eating difficulties in girls with Rett syndrome compared with other developmental disabilities. *J Am Diet Assoc* 2003;103:224–30.
7. Eltumi M, Sullivan PB. Nutritional management of the disabled child: the role of percutaneous endoscopic gastrostomy. *Dev Med Child Neurol* 1996;39:66–8.
8. Blackman JA, Nelson CL. Reinstituting oral feedings in children fed by gastrostomy tube. *Clin Pediatr* 1985;24:434–8.
9. Blackman JA, Nelson CL. Rapid introduction of oral feedings to tube-fed patients. *J Dev Behav Pediatr* 1987;8:63–7.
10. Weaving LS, Ellaway CJ, Gecz J, et al. Rett syndrome: clinical review and genetic update. *J Med Genet* 2005;42:1–7.
11. Budden S, Meek M, Henighan C. Communication and oral-motor function in Rett syndrome. *Dev Med Child Neurol* 1990;32:51–5.
12. Dickerson RN, Brown RO, Gervasio JG, et al. Measured energy expenditure of tube-fed patients with severe neurodevelopmental disabilities. *J Am Coll Nutrit* 1999;18:61–8.
13. Pearce C, Duncan H. Enteral feeding. Nasogastric, nasojejunal, percutaneous endoscopic gastrostomy, or jejunostomy: its indications and limitations. *Postgrad Med J* 2002;78:198–204.

14. Colvin L, Fyfe S, Leonard S, et al. Describing the phenotype in Rett syndrome using a population database. *Arch Dis Child* 2003; 88:38–43.
15. Laurvick CL, de Klerk N, Bower C, et al. Rett syndrome in Australia: a review of the epidemiology. *J Pediatr Child Health* 2006;148:347–52.
16. Laurvick CL, Msall ME, Silburn S, et al. Physical and mental health of mothers caring for a child with Rett syndrome. *Pediatrics* 2006;118:e1152–64.
17. Morton RE, Bonas R, Minford J, et al. Feeding ability in Rett syndrome. *Dev Med Child Neurol* 1997;39:331–5.
18. Centers for Disease Control. National Health and Nutrition Examination Survey. CDC Growth Charts: United States.Percentile Data Files with LMS Values. *http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm.* Accessed August 10, 2007.
19. Cole TJ, Faith MS, Pietrobelli A, et al. What is the best measure of adiposity change in growing children: BMI, BMI %, BMI z-score or BMI centile? *Eur J Clin Nutr* 2005;59:419–25.
20. Fredriks AM, van Buuren S, Burgmeijer RJ, et al. Continuing positive secular growth change in The Netherlands 1955–1997. *Pediatr Res* 2000;47:316–23.
21. Ellaway CJ, Peat J, Williams K, et al. Medium-term open label trial of L-carnitine in Rett syndrome. *Brain Dev* 2001;23 (Suppl 1): S85–9.
22. Weaving LS, Williamson SL, Bennetts B, et al. Effects of MECP2 mutation type, location and X-inactivation in modulating Rett syndrome phenotype. *Am J Med Genet* 2003;118:103–14.
23. Stata Corp, Stata Statistical Software version 9.0. College Station, TX: Stata Corp; 2005.
24. SPSS Inc, Windows version 11.0.0. Chicago: SPSS Inc; 2001.
25. Thommessen M, Kase BF, Heiberg A. Growth and nutrition in 10 girls with Rett Syndrome. *Acta Paediatr* 1992;81:686–90.
26. Smeets E, Terhal P, Casaer P, et al. Rett syndrome in females with CTS hot spot deletions: a disorder profile. *Am J Med Genet* 2005; 132:117–20.
27. Colvin L, Leonard H, de Klerk N, et al. Refining the phenotype of common mutations in Rett syndrome. *J Med Genet* 2004;41: 25–30.
28. Leonard H, Moore H, Carey M, et al. Genotype and early development in Rett syndrome: the value of international data. *Brain Dev* 2005;27:S59–68.
29. Schanen C, Houwink EJ, Dorrani N, et al. Phenotypic manifestations of MECP2 mutations in classical and atypical Rett syndrome. *Am J Med Genet A* 2004;126:129–40.
30. Jian L, Archer HL, Ravine D, et al. p.R270X MECP2 mutation and mortality in Rett syndrome. *Eur J Human Genet* 2005;13:1235–8.
31. Motil KJ, Schultz RJ, Wong WW, et al. Increased energy expenditure associated with repetitive involuntary movement does not contribute to growth failure in girls with Rett syndrome. *J Pediatr* 1998;132: 228–33.
32. Motil KJ, Schultz R, Brown B, et al. Altered energy balance may account for growth failure in Rett Syndrome. *J Child Neurol* 1994;9: 315–9.
33. Budden S. Management of Rett syndrome: a ten year experience. *Neuropediatrics* 1995;26:75–7.
34. Budden SS. Rett-syndrome—habilitation and management reviewed. *Eur Child Adolesc Psychiatry* 1997;6 (Suppl 1):103–7.
35. Motil KJ, Schultz RJ, Browning K, et al. Oropharyngeal dysfunction and gastroesophageal dysmotility are present in girls and women with Rett syndrome. *J Paediat Gastroenterol Nutr* 1999;29:31–7.
36. Stallings VA, Zemel BS, Davies JC, et al. Energy expenditure of children and adolescents with severe disabilities: a cerebral palsy model. *Am J Clin Nutr* 1996;64:627–34.
37. Fitzgerald PM, Jankovic J, Glaze DG, et al. Extrapyramidal involvement in Rett's syndrome. *Neurol* 1990;40:293–5.
38. Witt Engerström I. Age-related occurrence of signs and symptoms in the Rett syndrome. *Brain Dev* 1992;14:S11–20.
39. Craig GM, Carr LJ, Cass H, et al. Medical, surgical, and health outcomes of gastrostomy feeding. *Dev Med Child Neurol* 2006;48: 353–60.
40. Corwin DS, Isaacs JS, Georgeson KE, et al. Weight and length increases in children after gastrostomy placement. *J Am Diet Assoc* 1996;96:874–9.
41. Sullivan P, Juszczak E, Bachlet A, et al. Impact of gastrostomy tube feeding on the quality of life of carers of children with cerebral palsy. *Dev Med Child Neurol* 2004;46:796–800.