Impact of Gastrostomy Placement on Nutritional Status, Physical Health, and Parental Well-Being of Females with Rett Syndrome: A Longitudinal Study of an Australian Population

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Objectives To evaluate how age-related trends in nutritional status, physical health, and parental well-being in females with Rett syndrome may be related to gastrostomy placement and to examine the impact of the procedure on mortality.

Study design We included 323 females from the Australian Rett Syndrome Study and analyzed their demographic, genetic, and child and parental health data collected from over 6 waves of follow-up questionnaire between 2000 and 2011. We used mixed-effects models to estimate the association between repeated measures of outcomes and age, gastrostomy placement and their interaction and Cox proportional hazards regression models to estimate relative risks of mortality for individuals with gastrostomy.

Results Nearly one-third (30.3%) of the cases underwent gastrostomy placement. Nutritional status based on weight, height, and body mass index (BMI) improved over time, and BMI was greater in individuals with gastrostomy placement than in those without (adjusted $\beta = 0.87$, 95% CI 0.02-1.73). There was no association between gastrostomy placement and individual's physical health outcomes or parental physical and mental health, nor did the age trend of these outcomes vary by gastrostomy insertion status. Nevertheless, among those at risk of suboptimal weight, the all-cause mortality rate was greater in those who had gastrostomy placement compared with those who had not (hazard ratio 4.07, 95% CI 1.96-8.45).

Conclusion Gastrostomy placement was associated with improvement in BMI in females with Rett syndrome, but its long-term impact on individuals and their families is unclear. *(J Pediatr 2018;■■:■■-■■).*

Rett syndrome is a rare but severe neurodevelopmental disorder mainly seen in females.[1] The estimated incidence is 1 in 8500 female births.[2] It is associated with severe disability, and there is no specific treatment or cure. Until recently, epidemiologic and outcome data have been relatively sparse.

The main diagnostic criteria of classical Rett syndrome now include a history of partial or complete loss of acquired purposeful hand skills; a history of loss of acquired spoken language; impairment or inability to walk; and the presence of stereotypic hand movements.[3] Comorbidities include scoliosis, poor growth, osteoporosis, epilepsy, breathing abnormalities, and sleep difficulties.[4] In 1999, a causal association was identified between Rett syndrome and mutations in the methyl CpG binding protein 2 (*MECP2*) gene,[5] and now more than 500 disease-causing *MECP2* mutations have been reported.[6]

Feeding difficulties and poor growth commonly are seen in Rett syndrome and may be associated with poor oro-motor function, limited self-feeding skills, gastroesophageal reflux disease, breathing dysfunction, and constipation.[7-9] There is a progressive decline in height, weight, and body mass index (BMI) with age, likely influenced by genotype.[10,11] Gastrostomy feeding tube placement is a therapeutic option for addressing feeding difficulties and poor nutritional status. To date, its effectiveness in Rett syndrome has been studied only in a US clinic–based series, where the outcomes assessed were limited to anthropometric data without consideration of other aspects of quality of care, such as child and parental well-being.[12] In keeping with the quality-of-care literature[13] and recent recommendations

BMI	Body mass index
IRR	Incidence rate ratio
MCS	Mental Component Summary
MECP2	Methyl CpG binding protein 2
PCS	Physical Component Summary
WAZ	Weight-for-age z score

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relating to the assessment of gastrostomy outcomes,[14] the aims of this study were to investigate age-related trends in nutritional status, physical health, and parental well-being in individuals with Rett syndrome and to evaluate how these changes may be related to gastrostomy placement. We also examined the impact of gastrostomy on mortality.

Methods

Established in 1993, the Australian Rett Syndrome Study began recruiting individuals with Rett syndrome from cases identified through the Australian Paediatric Surveillance Unit, the Rett Syndrome Association of Australia, and other sources,[15] including clinicians who manage the 3 specialized Rett syndrome clinics in Sydney, Melbourne, and Perth. At the core of the current study is the Australian Rett Syndrome Database, which stores demographic, genetic, and health data on individuals with Rett syndrome at the time of recruitment, as well as responses from parents/caregivers to follow-up questionnaires that have been administered to primary caregivers since 1996. From 2000 onwards, questionnaires have included measures of functional ability; behavior and hand function; information on medical conditions; episodes of illness; use of health, therapy, respite, and daycare services; feeding; equipment use; and education. From 2002 onwards, questionnaires also have included measures of family functioning and health and well-being of the primary caregiver (eg, parents). Seven waves of follow-up questionnaires (1996, 2000, 2002, 2004, 2006, 2009, and 2011) have been distributed. Pertinent clinical data, including data recorded during inpatient care and outpatient attendance, were extracted from medical records to enrich the dataset captured by the questionnaire.

Ethics approval for data collection was provided by the Human Research Ethics Committee of Princess Margaret Hospital for Children, Perth (1909/EP); Royal Perth Hospital, Perth (RA-12/007); Women's and Children's Hospital, Adelaide (HREC/13/WCHN/57); Royal Children's Hospital, Melbourne (31339A); Monash Medical Centre, Melbourne (14203Q); Sydney Children's Hospitals Network, Sydney (LNR-2011-10-13); Mater Children's Hospital, Brisbane (1878/LNR); and Royal Children's Hospital, Brisbane (HREC/12/QRCH/76). Ethics approval also was obtained to link the cohort to the National Death Index administered by the Australian Institute of Health and Welfare (EC380). All families provided informed consent before participating. The study design can be considered as a single-cohort, multiple-age design, a variant of the cross-sequential longitudinal design.[16]

Study Participants

Females with a clinically or genetically confirmed diagnosis of Rett syndrome whose parents/caregivers had completed at least 1 follow-up questionnaire from 2000 were included in the study. Health outcomes, including individuals' anthropometric and physical health data, were collected from questionnaires in 2000, 2002, 2004, 2006, 2009, and 2011 and hospital records, whereas data on parental well-being outcomes were gathered from questionnaires in 2002, 2006, 2009, and 2011. For health outcomes, 323 individuals with Rett syndrome were eligible for the study. The number of questionnaires completed ranged from 1 to 6 with a median of 3. A total of 88 parents/caregivers completed all 6 waves of questionnaires, 47 had completed 4, 44 had completed 4, 40 had completed 3, 53 had completed 2, and 51 had completed 1. Therefore, a total number of 1216 responses were available for 323 individuals. For parental well-being outcomes, parents/caregivers of 311 individuals completed at least 1 of the 4 waves of questionnaires. The number of questionnaires completed ranged from 2 to 4 per individual with a median of 2. A total of 116 parents/caregivers had completed all 4 questionnaires, 70 completed 3, 57 completed 2, and 68 completed 1. The total numbers of individuals and responses were 311 and 856, respectively.

Variable Definitions

Weight (kg) and height (cm) data were provided by parents/caregivers in the follow-up questionnaires, in addition to those ascertained from medical records. BMI (kg/m^2) was calculated as weight divided by height squared. Parental well-being was measured using the 12-Item Short-Form Health Survey Physical Component Summary (PCS) and Mental Component Summary (MCS) scales, with greater scores representing better health.[17] The PCS domains are named as follows: "Physical Functioning," "Role-physical," "Bodily Pain," and "General Health," whereas the MCS domains are "Vitality," "Social Functioning," "Role-emotional," and "Mental Health." The instrument was included in the 2002, 2006, 2009, and 2011 follow-up questionnaires and was answered by either parent of the individual. The PCS and MCS scores have been shown to be valid in Australian and other populations.[18,19] Using the population mean item weight method, data with up to 3 of the 6 key items (ie, items that contribute predominantly to a given score) missing and any number of non-key items missing for either PCS or MCS were imputed.[20] Total number of illness episodes was defined as the sum of the reported number of upper (eg, cold, ear infection, tonsillitis) and lower (eg, bronchitis, pneumonia) respiratory infections experienced by the individual in the 12 months before completion of each follow-up questionnaire. Cumulative length of hospital stay was defined as the sum of reported number of days in hospital being admitted for respiratory tract infections, seizures, or gastrointestinal problems in the 12 months before completion of the follow-up questionnaire.

Gastrostomy placement was defined by whether the intervention had been reported at the time of the follow-up questionnaire completion and was coded as a binary variable: yes/no. Other variables included in the analysis were age at completion of each questionnaire centered on an overall median value of 15 years, *MECP2* gene mutation type, feeding method, mobility, ever learned to walk, sleep disturbances, scoliosis, and breath holding. Family variables included in the analysis were residence, type of respondent, respondent's age, respondent's work status, respondent's highest level of education, use of formal respite care, household annual income, geographic

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