Pediatric Neurology 53 (2015) 402–411

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

The Changing Face of Survival in Rett Syndrome and *MECP2*-Related Disorders

Daniel C. Tarquinio DO [a], Wei Hou PhD [b], Jeffrey L. Neul MD, PhD [c], Walter E. Kaufmann MD, PhD [d], Daniel G. Glaze MD [c], Kathleen J. Motil MD, PhD [c], Steven A. Skinner MD [e], Hye-Seung Lee PhD [f], Alan K. Percy MD [g,*]

[a] *Department of Pediatrics, Emory University, Atlanta, Georgia*
[b] *Stony Brook University Medical Center, Stony Brook, New York*
[c] *Department of Pediatrics, Duncan Neurological Research Institute, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas*
[d] *Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts*
[e] *Greenwood Genetic Center, Greenwood, South Carolina*
[f] *Pediatrics Epidemiology Center, University of South Florida, Tampa, Florida*
[g] *Civitan International Research Center, University of Alabama at Birmingham, Alabama*

ABSTRACT

PURPOSE: Survival in Rett syndrome remains unclear. Although early estimates were grim, more recent data suggest that survival into adulthood is typical. We aimed to define survival in Rett syndrome more clearly and identify risk factors for early death. **METHODS:** Participants with clinical Rett Syndrome or *methyl-CpG-binding protein 2* mutations without clinical RTT were recruited through the Rett Syndrome Natural History study from 2006 to 2015. Clinical details were collected, and survival was determined using the Kaplan-Meier estimator. Risk factors were assessed using Cox proportional hazards models. **RESULTS:** Among 1189 valid participants, 51 died (range 3.9-66.6 years) during the 9-year follow-up period. Those who died included 36 (3.9%) classic Rett syndrome females, 5 (5.9%) atypical severe Rett syndrome females, 1 (2.4%) non-Rett syndrome female, the single atypical severe male, 6 (30%) non-Rett syndrome males, and 2 (7.1%) *methyl-CpG-binding protein 2* duplication syndrome males. All atypical mild Rett syndrome females, *methyl-CpG-binding protein 2* duplication syndrome females, and the single classic Rett syndrome male remain alive. Most deaths were due to cardiorespiratory issues. Only one died from severe malnutrition, scoliosis, and extreme frailty. Survival for classic and atypical Rett syndrome was greater than 70% at 45 years. Overall severity and several modifiable risk factors, including ambulation, weight, and seizures, were associated with mortality in classic Rett syndrome. **CONCLUSIONS:** Survival into the fifth decade is typical in Rett syndrome, and death due to extreme frailty has become rare. Although the leading cause of death remains cardiorespiratory compromise, many risk factors for early death are modifiable. Intense therapeutic interventions could further improve the prognosis for individuals with Rett syndrome.

Keywords: Rett syndrome, risk factors, prognosis, survival, mortality

Pediatr Neurol 2015; 53: 402-411

Introduction

The report of Hagberg et al. in 1983 provided the first widely read English-language publication on Rett syndrome (RTT), resulting in the remarkable expansion of clinical studies to understand the specific features of this X-linked dominant disorder. The identification of mutations in *methyl-CpG-binding protein 2* (*MECP2*) in 1999 allowed

Article History:
Received May 22, 2015; Accepted in final form June 5, 2015
* Communications should be addressed to: Dr. Percy; 1720 2nd Avenue South; CIRC 320E; Birmingham, AL 35294-0021.
E-mail address: apercy@uab.edu

0887-8994/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2015.06.003

fundamental research to progress dramatically. However, increased recognition of the disorder, expansion of the scope of clinical assessments, and the active involvement of parents and other caregivers worldwide had begun to alter the extent of clinical involvement in the management of this unique neurodevelopmental disorder before 1999.[1] Early longitudinal studies[2] revealed that after the initial stagnation and regression of development, children reach a "steady state" in adolescence and adulthood. Neuropathological studies[3] shifted the perception from "degenerative" to the current perspective of a neurodevelopmental disorder.[4] With increasing recognition of the myriad clinical issues and the need for intense therapeutic approaches, longevity and overall quality of life improved.[5] The predominant morbidity issues include growth,[6] nutrition,[7] scoliosis,[8] seizures,[9] aspiration risk, and gastrointestinal dysfunction (gastroesophageal reflux, delayed gastric emptying, and constipation).[10] Clinical experience suggests that intense physical and occupational therapies reduced development of contractures and skeletal deformities and communication technologies improve engagement.

The initial report of deaths in RTT occurred before implementation of intense therapeutic approaches.[11] Thus, of the reported deaths, half were attributed to frailty and debilitation with frequent aspiration and 25% were attributed to an unwitnessed event assumed to be related to seizures or aspiration. More than 10 years later, the first survival study, conducted among more than 1900 participants in the United States and Canada indicated 50% survival at 50 years.[5] Shortly thereafter, an analysis of the original cohort seen by Rett indicated a much reduced survival rate.[12] The same report, together with a recent study providing data from Australia,[13] yield similar results to those from the United States and Canada.

In this report, we show that survival from the US RTT Natural History Study (RNHS) is somewhat better than the 2010 survival study.[5] Using the detailed clinical data in the RNHS, we have analyzed the 52 deaths reported in this cohort; together, these represented 4.3% of those enrolled. In contrast to the 1997 study, only one of these was related to a debilitated condition. We sought to identify characteristics associated with greater likelihood of death.

Methods

Participants

Through the multicenter RNHS, individuals with clinical RTT were recruited from March 2006 until February 2015 and evaluated at one of eight United States sites every 6 to 12 months, as described previously.[6,9] The RNHS consortium is part of the Rare Diseases Clinical Research Network, an initiative of the Office of Rare Diseases Research, National Center for Advancing Translational Sciences. An RNHS neurologist or geneticist (J.L.N., W.E.K., D.G.G., S.A.S., and A.K.P.) confirmed the diagnosis based upon diagnostic criteria.[14,15] Two scales were used to assess overall severity, the clinical severity scale and motor behavioral assessment, and quality of life was assessed using the Child Health Questionnaire 50 as previously reported.[6] Reports of electrocardiographs were collected and QT and corrected QT (QTc) intervals were recorded. All participants had *MECP2* testing by a qualified laboratory. Although more than 95% of those with classic RTT have a mutation, participants with clinical RTT were included even if they lacked a mutation. Deaths and related events indicative of causation were assessed from participants with classic RTT, atypical RTT, those who had mutations in *MECP2* but did not meet criteria for classic or atypical RTT (non-RTT), and those with *MECP2* duplication syndrome (DUP). Death certificates were reviewed and details extracted; additional information was collected from caregivers on events preceding death. The first contact with the RNHS was used as the point of entry, and the last contact or age at death was used as the study exit point.

Data categorization

Atypical RTT typically presents in two ways: the first scenario is an individual who achieved few early skills and, with fewer skills to lose, did not express regression in either language or hand use, generally with a more severe disease course; the second scenario is an individual who acquired language and hand use either on time or with some delay, and did not experience regression in hand use or language, generally with a less severe disease course. The clinical severity score in atypical RTT has a bimodal distribution, with nadir at 21; therefore, these two groups were divided into atypical mild (clinical severity scale $\leq$20) and atypical severe (clinical severity scale $\geq$21).[16] Ambulation was categorized in a binary (able to stand or walk, unable to stand or walk) and ordinal fashion. Epilepsy was categorized in a binary (those with seizures despite medical management, and those with well controlled or no seizures) and ordinal fashion. Other characteristics and comorbidities (e.g., breathing dysregulation) were characterized based on frequency during examination, and socioeconomic status was categorized into ordinal groups based on comparison to the national median income. Interval of QTc was categorized into normal ($\leq$450), borderline (451-<470) and abnormal (>470). Growth parameters (height, weight, body mass index, head circumference) were categorized using both normative[17,18] and Rett-specific z scores. The standard cutoffs of $\pm$2 standard deviation (approximating the second and 98th percentiles) were used for normative charts and more liberal cutoffs of $-$1.28 standard deviation (10th percentile) and $-$0.67 standard deviation (25th percentile) on RTT charts were tested, in keeping with recent recommendations.[7] Mutation severity was categorized into mild (R133C, R294X, R306C, and 3′ truncations) and severe (T158M, R168X, R255X, and R270X) *MECP2* mutations.[19]

Statistical analysis

Descriptive statistics included age, *MECP2* status, growth, motor behavioral assessment and clinical severity scale, number who died, and causation of death. Survival was calculated using the Kaplan-Meier estimator, conditional upon survival up to initial encounter. The association of categorical or ordinal variables (growth, mutation type, race, ethnicity, socioeconomic status, ability to walk, scoliosis, breathing dysregulation, sleep disturbance, hand function, frequency of stereotypies, tone, reflexes, autonomic dysfunction, epilepsy) and continuous variables (quality of life, number of hospitalizations or fractures, motor behavioral assessment and clinical severity scale) with survival was assessed by fitting to Cox proportional hazards models. Survival was compared among diagnostic categories using the log-rank test, and significant predictors in the Cox models were plotted as individual survival curves. Nonparametric data were summarized using the median and interquartile range. Statistical analyses were performed using SPSS.[20]

Human studies approval

Each site obtained and maintained institutional review board approval for the performance of this study. Parental approval for study conduct and publication of results was obtained before entry into the study. The study has been registered with ClinicalTrials.gov: NCT00299312 since March 3, 2006.

Results

Overall, 1205 individuals were enrolled in the RNHS. Diagnosis could not be verified on 14. Two with *CDKL5*

mutation and atypical RTT were excluded from further analysis; one of these died at age 6.9 years of age from presumed cardiac arrest. Fifty-one deaths occurred in the remaining cohort of 1189 participants; these were followed for up to 9.0 years (median 7.0 years), and included 925 with classic RTT (one male), 80 females with atypical mild RTT, 86 with atypical severe RTT (one male), 62 non-RTT (20 males), and 36 DUP (28 males). Of the female participants, 36 (3.9%) with classic RTT, five (5.9%) with atypical severe RTT, and one non-RTT female (2.4%) died during the study. Of the male participants, the single atypical severe male, six (30%) of the non-RTT males and two (7.1%) of the DUP males died. All of the atypical mild RTT females, DUP females and the single classic RTT male remain alive. None born after 1997 lived in a group home or institution. The proportion of those older than 18 years who lived in a group home was 7.3%; in an institution, 1.2%.

The causes of death divided by diagnostic category are listed in Table 1. According to death certificates, of those with classic RTT with an unknown cause of death, the majority was presumed to be related to cardiac arrest or respiratory compromise secondary to aspiration or pneumonia; four occurred at night and were unwitnessed. Postoperative complications were a cause of death in a minority, following scoliosis surgery, ileostomy, and tonsillectomy. Epilepsy was cited as cause of death (without respiratory complications) in four classic RTT participants and one atypical RTT participant. Additionally, the non-RTT male who died after vagus nerve stimulation placement had experienced worsening seizures for several months, and then developed cardiac dysrhythmia in the operating room. For atypical RTT, the two with unknown cause of death were presumed to be due to aspiration. One of those with atypical RTT who died with overwhelming infection was regarded as severely malnourished with severe scoliosis resulting in organ displacement and an extremely frail condition.

Considering age of death among the 1089 participants with classic and atypical RTT, the youngest died at age 3.85 years and the oldest at age 66.6 years. The proportion of mortality in classic and atypical severe RTT overall was similar (Fig 1). The latter contrasts with zero mortality among the 80 atypical mild participants. Kaplan-Meier curves revealed that the proportion of participants remaining alive in both classic and atypical severe RTT, including the 95% confidence intervals (CI), was greater than 70% at 45 years. However, too few participants were recruited after age 45 years for accurate estimation. Although many male participants with *MECP2* mutation died before age 10, none with DUP died during childhood (Fig 2).

Of the 613 participants with classic and atypical RTT who had electrocardiograph data, 18% had a borderline and 10% had an abnormal QTc interval. However, the proportion with a borderline or abnormal electrocardiograph was similar between those who died (21%) and those who

TABLE 1.
Cause of Death Based on Diagnostic Category (Total n = 1189)

Diagnosis	Number with Diagnosis	Cause of Death	Number who Died	% Within Category
Classic female	924		36	
		Epilepsy	4	11.1
		Respiratory (± aspiration/pneumonia)	5	13.9
		Infection*	4	11.1
		Postoperative complications†	4	11.1
		Unknown (unspecified)	3	8.3
		Unknown nocturnal	4	11.1
		Unknown presumed cardiorespiratory	12	33.3
Atypical mild female	80		0	
Atypical severe female	85		5	
		Unknown nocturnal (presumed cardiorespiratory/epilepsy)	1	20.0
		Unknown presumed cardiorespiratory	1	20.0
		Respiratory (pneumonia, restrictive lung disease)	2	40.0
		Malnutrition, scoliosis, pneumonia	1	20.0
Non-Rett female	42		1	
		Hyperkalemia	1	100.0
Duplication female	8		0	
Classic male	1		0	
Atypical severe male	1		1	
		Respiratory (pneumonia)	1	100.0
Non-Rett mutation male	20		6	
		Respiratory (aspiration)	1	16.7
		Postoperative complications‡	1	16.7
		Unknown (unspecified)	1	16.7
		Unknown presumed cardiorespiratory	3	50.0
Non-Rett duplication male	28		2	
		Unknown (unspecified)	1	50.0
		Unknown presumed cardiorespiratory	1	50.0

* Chronic urinary tract infection, cystic fibrosis–related pneumonia, chronic infection leading to sepsis and renal failure.
† Ileostomy, spinal fusion, tonsillectomy.
‡ Vagus nerve stimulation placement.

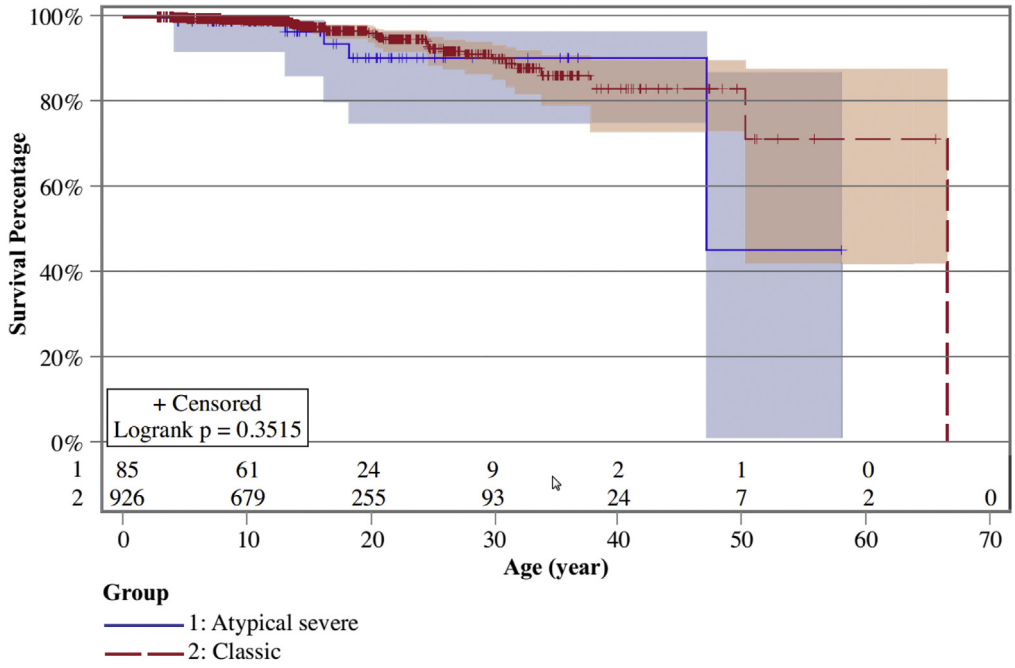

FIGURE 1.
Survival in classic and atypical severe Rett syndrome. Survival was similar in classic and atypical severe Rett syndrome until age 45 years including median and 95% confidence interval (Hall-Wellner bands). After 45 years, data were too sparse and confidence intervals too wide for meaningful comparison. (The color version of this figure is available in the online edition.)

survived to the end of the study (29%, $P = 0.47$). Ninety-seven percent of those with classic RTT had a mutation in *MECP2*; 33 (3.7%) of those with a mutation died, whereas three (9.7%) of those without a mutation died. Only 68% of those with atypical severe RTT had a *MECP2* mutation, but all atypical severe RTT participants who died had a mutation. Specific *MECP2* mutations were not significantly associated with mortality. However, in those with classic

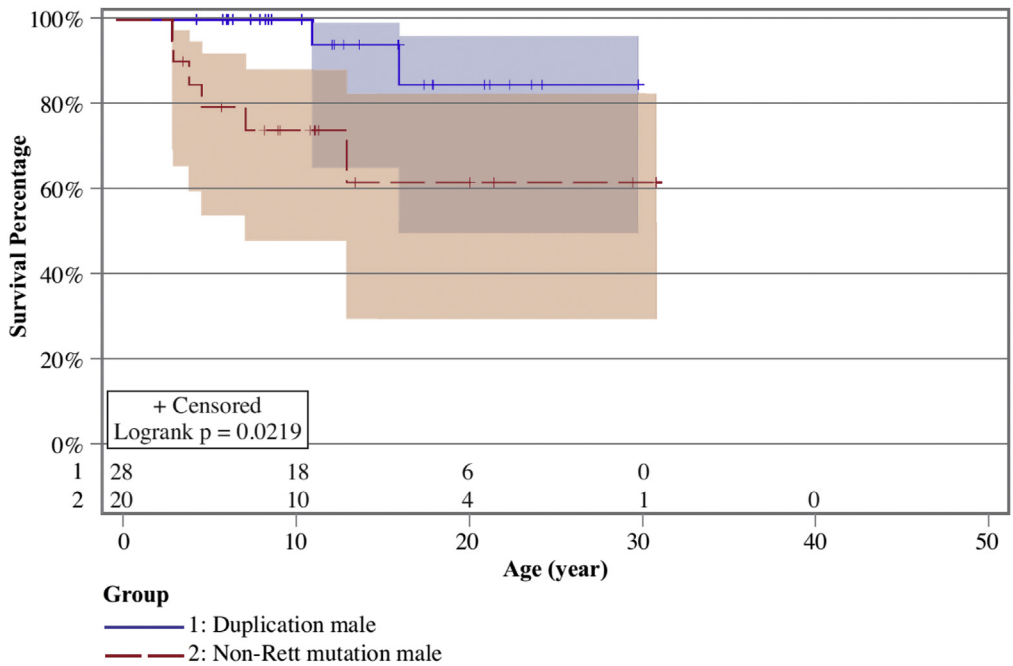

FIGURE 2.
Survival of non-Rett syndrome (RTT), *methyl-CpG-binding protein 2* (*MECP2*)-positive males, and duplication (DUP)males. Few non-RTT males and DUP participants were recruited and confidence intervals are wide (95% Hall-Wellner bands. However, survival was generally better in DUP participants and poorer in non-RTT male participants. (The color version of this figure is available in the online edition.)

TABLE 2.
Deaths in Classic RTT Among Specific *MECP2* Mutations (n = 885)

Mutation Category	MECP2 Mutation	Total n	Number who Died	%
Mild mutations	R133C	41	1	2.4
	R294X	53	4	7.0
	R306C	60	3	4.8
	3′ Truncation	78	1	1.3
Severe mutations	R106W	25	1	3.8
	T158M	95	5	5.0
	R168X	95	3	3.1
	R255X	86	1	1.1
	R270X	51	3	5.6
	Large deletion	75	6	7.4
Miscellaneous mutations	Other point mutation	97	3	3.0
	Insertion	20	0	0.0
	Deletion	51	2	3.8
	Exon 1	4	0	0.0
	Splice site	9	0	0.0
	Multiple mutations	12	0	0.0

Abbreviations:
MECP2 = *methyl-CpG-binding protein 2*
RTT = Rett syndrome
Missing or unclear data in 8 patients.

RTT, large deletions (7.4%) and R294X (7.0%) had the highest frequency of deaths, nearly double the average of all mutations groups combined (3.9%) and three times the frequency with R133 C (2.4%, Table 2). Nine (3.7%) in the mild and 19 (4.3%) in the severe mutation categories died during the study. For other diagnostic categories, the numbers were too small to consider a comparison.

Growth in classic RTT

Differences in mortality were more profound when the RTT-specific charts were used and are reported here, although differences in height and weight were also seen on normative charts. Mortality was similar for those with normal and low body mass index. However, the majority of those who died (54%, or 19/35) weighed less than the 25th percentile on the Rett-specific charts, compared with 22% of those who survived ($P < 0.001$). Additionally, the majority of those who died (57%, or 20/35) measured less than the 25th percentile for height on the Rett-specific charts, compared with 23% of those who survived ($P < 0.001$). The proportion of those with a smaller head (<25th percentile) on the Rett-specific charts was 40% for those who died (14/35) compared with 22% (187/862) for those who survived ($P = 0.01$).

Risk factors for mortality

In classic RTT, median scores on one or both of the two severity scales were higher in those who died compared with those who were living at the end of the study (Table 3). In atypical severe RTT and male DUP patients, severity was higher on one of the two scales but not the other in those who died. For classic RTT, several variables, such as ambulation, frequent seizures, frequent hospitalizations and illness, microcephaly, and low weight, were independently associated with higher odds of mortality using a Cox proportional hazard model (Table 4). Many of the categorical variables associated with increased odds of mortality also revealed significant differences when

TABLE 3.
Median Severity Scores and Mortality

Diagnosis	Severity Scale	Survival	N	Median	Interquartile Range	Minimum	Maximum	Mean Severity Rank	Mann-Whitney *P*-value
Classic RTT	CSS	Alive at end	858	25	20-31	5	45	435	
		Died before end	35	35	29-37	20	43	730	<0.001
	MBA	Alive at end	861	54	44-64	12	96	439	
		Died before end	35	68	61-73	49	95	689	<0.001
Atypical severe RTT	CSS	Alive at end	76	31	27-34	22	47	41	
		Died before end	5	31	29-36	27	38	45	0.68
	MBA	Alive at end	76	59	51-65	23	88	40	
		Died before end	5	81	57-86	46	87	61	0.04
Non-RTT female	CSS	Alive at end	39	7	2-10	0	41	21	
		Died before end	1	1	N/A	N/A	N/A	6	0.30
	MBA	Alive at end	39	13	7-25	0	69	21	
		Died before end	1	3	N/A	N/A	N/A	7	0.35
Non-RTT male	CSS	Alive at end	13	25	15-36	9	39	14	
		Died before end	6	37	26-43	23	44	8	0.06
	MBA	Alive at end	14	50	42-77	22	78	13	
		Died before end	6	71	57-77	45	81	9	0.24
DUP male	CSS	Alive at end	26	14	10-21	6	32	14	
		Died before end	2	27	N/A	27	27	26	0.05
	MBA	Alive at end	26	42	22-52	5	80	14	
		Died before end	2	64	N/A	61	66	25	0.06

Abbreviations:
CSS = Clinical severity scale
DUP = Duplication syndrome
MBA = Motor behavioral assessment
MECP2 = *methyl-CpG-binding protein 2*
N/A = Not available
RTT = Rett syndrome
CSS is scored from 0 to 58 and MBA is scored from 0 to 148; higher scores on both indicate greater severity.

TABLE 4.
Risk factors for mortality in classic RTT

Variable	N	Hazard Ratio	95% Confidence Interval	*P*-value
Inability to walk*	882	3.2	1.6-6.5	0.00
Number of hospitalizations	892	1.1	1.0-1.2	0.00
Microcephalic	819	9.9	1.7-58.0	0.01
Poor global health†	813	1.8	1.1-3.1	0.02
Seizure severity‡	892	2.4	1.0-6.8	0.03
Unable to babble or use some words	819	2.6	1.1-6.5	0.03
Degree of rigidity‡	882	1.3	1.0-1.7	0.04
Poor hand use‡	882	2.6	1.0-6.8	0.05
Low weight Z score based on RTT references	854	2.9	1.0-8.8	0.05
Poverty§	819	7.4	0.9-60.5	0.06
Unable to sit independently*	882	1.3	1.0-1.6	0.07
Immunity†	813	1.4	1.0-1.9	0.07
Degree of dystonia‡	882	1.4	1.0-2.1	0.09

Abbreviations:
CHQ = Child Health Questionnaire
CSS = Clinical severity scale
MBA = Motor behavioral assessment
RTT = Rett syndrome
* CSS.
† CHQ.
‡ MBA.
§ Categories based on national median.

Kaplan-Meier curves were compared (Fig 3). For atypical severe RTT, only number of hospitalizations was associated with higher mortality (hazard ratio 2.6, 95% CI 1.1-6.3, $P = 0.03$). No significant associations were found between risk factors and mortality for other diagnostic categories, notably scoliosis, sleep disturbance, autonomic dysfunction, frequent fractures, hyperventilation or breath-holding.

Discussion

Compared to the initial report of Kerr et al. in 1997, in which nearly 50% of deaths were attributed to a frail or debilitated state with recurrent aspiration and pneumonia, our study has revealed a striking difference in the general health of participants.[11] Only one of the individuals in our cohort died as the result of a frail condition. Fifty of the fifty-seven reported causes of death in the 2014 Australian study of survival in RTT were similar to those reported here and specifically did not mention frailty or debilitation.[13] The cause of death in the majority of both ours and the Australian cohorts was presumed or confirmed cardio-respiratory issues, often due to aspiration. Prolonged QTc has received much attention in RTT, and, indeed, we found a striking prevalence of borderline and abnormal QTc intervals.[21] However, the proportion of those with an abnormal QTc interval was nonsignificantly lower in those who died. Therefore, although many died of unknown, "presumed" cardio-respiratory events, QTc prolongation was not a strong contributor.

We have demonstrated that several modifiable risk factors are independently associated with risk for mortality. These results strongly support the need for physicians to provide close overall supervision for nutrition, gastrointestinal issues (gastroesophageal reflux, constipation, or even gallbladder dysfunction), scoliosis monitoring, aspiration risk, and epilepsy. Additionally, physicians and parents should continue demanding intense therapeutic approaches not only during the school age years but also throughout life. Attention to proper and continued implementation of strong therapeutic practices to prevent or manage contractures, dystonic postures, and proper positioning will minimize risk factors for mortality such as rigidity and dystonia. Moreover, such therapy can help to maintain a proper level of engagement with family and peers, improving quality of life as patients age. Studies from both Australia and the US provide evidence of the benefit of proper surveillance which should continue to improve with the broadening awareness of this neurodevelopmental disorder.

Despite the grim picture painted by Rett's original cohort, both ours and the Australian cohorts indicate that survival into adulthood is typical.[12] Additionally, remarkable cases of older patients with RTT exist. One woman with RTT survived until age 79, dying of post-operative complications.[22,23] Another woman diagnosed at age 52 years who had not walked or used her hands in over 20 years regained the ability to walk independently and feed herself with her hands through intense therapy.[24] Cross-sectional studies suggest that women with RTT are generally healthy, and may improve with respect to function and comorbidities during adolescence and adulthood.[25,26] Yet, few longitudinal studies have examined survival or risk factors for mortality in RTT. In a cohort of 53 Dutch adult women with RTT, only 37 were successfully followed for 5 years, and 7 died.[27] Within this cohort, cognitive function appeared to be preserved, overall health was good, and comorbidities such as epilepsy and autonomic dysfunction stabilized or decreased over time in most. Only slight motor decline occurred over 5 years on average. Most hospitalizations were for pneumonia, but cause of death was often sudden and unclear. A recent population-based study of the 102 patients diagnosed with RTT in Serbia also found the leading cause of death among the 19 patients who died to be pneumonia.[28] This cohort was relatively young, the oldest being 31 years old, and their incidence of 0.59:10,000 female live births is lower than that of larger studies, suggesting that many patients remain undiagnosed in that country.[29,30] With up to 20 years of follow-up data, the Australian cohort remains the most robust sample from a longitudinal standpoint. However, this sample of almost 400 participants is substantially smaller than ours, and rate of death was higher overall. The Australian study examined the associations between *MECP2* mutation and various comorbidities, but not the mortality risk conferred by specific features or comorbidities.

Ours is the first study of survival with an assessment of all participants directly examined by a Rett syndrome specialist, and the first to examine mortality risk associated with RTT phenotype. The 2010 US study of survival included a subpopulation of those in the current study (less than 1/3 of the current cohort) followed for less than 2 years, but found somewhat lower survival overall in classic RTT (approximately 60% at 40 years and 45% at

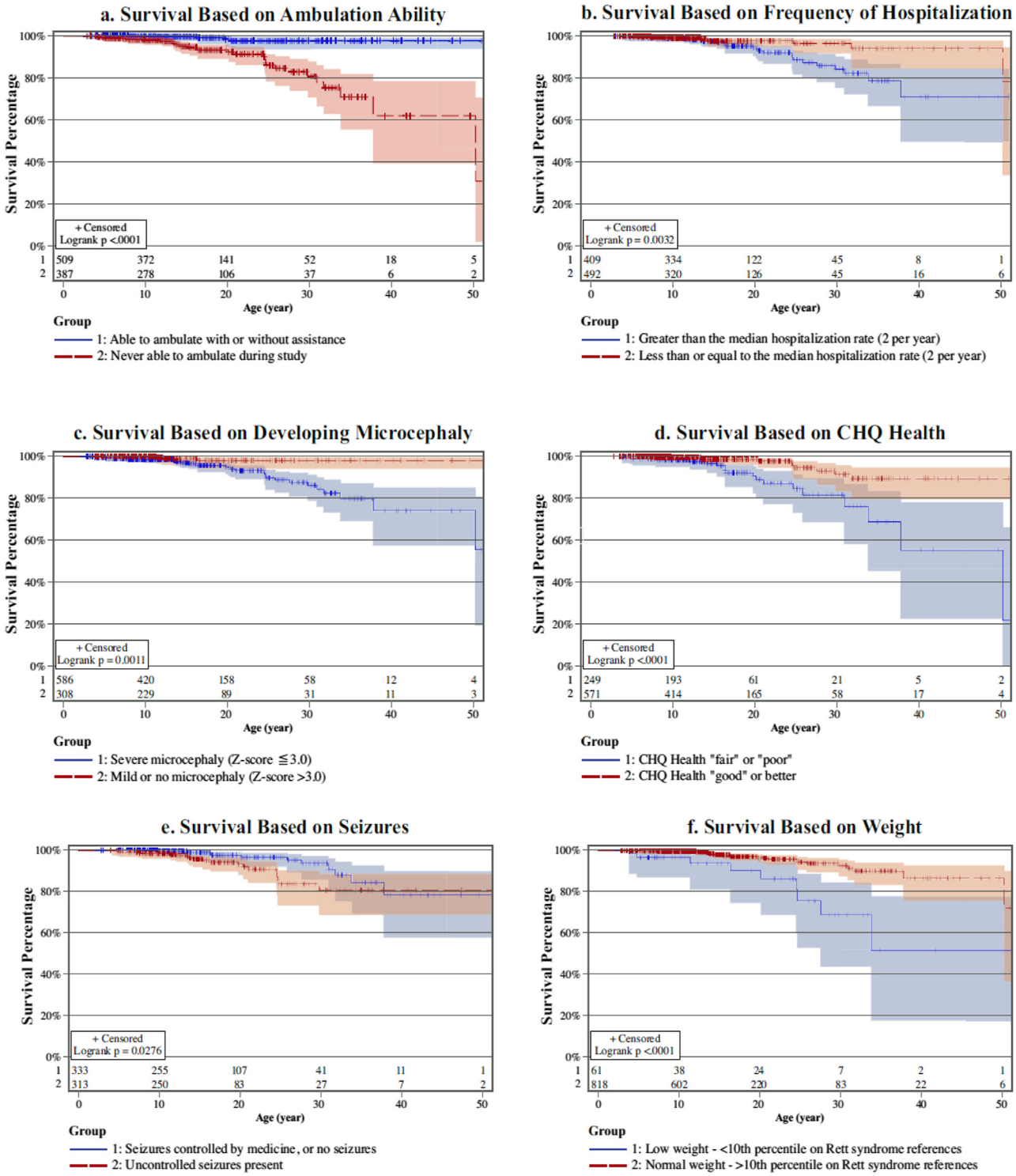

FIGURE 3.
Categorical risk factors for mortality in classic Rett syndrome. Several variables were independently associated with survival. (A) Survival based on ambulation ability. (B) Survival based on frequency of hospitalization. (C) Survival based on developing microencephaly. (D) Survival based on the Child Health Questionnaire (CHQ). (E) Survival based on seizures. (F) Survival based on weight. (G) Survival based on income. (H) Survival based on sitting. (I) Survival based on immune system. (J) Survival based on dystonia. All variables displayed were also significant independent predictors in Cox regression (Table 4). Median and 95% confidence intervals (Hall-Wellner bands) displayed for each, with *P*-values of log-rank test. (The color version of this figure is available in the online edition.)

50 years).[5] Survival in the atypical RTT group was found to be significantly better than in classic RTT; however, this was likely due to the inclusion of both mild atypical and severe atypical individuals in the same group. Although categorizing mild and severe individuals together as "atypical" has been done since the 1995 diagnostic criteria defined atypical RTT, atypical mild participants rarely die prematurely. This disparity lends more support to the

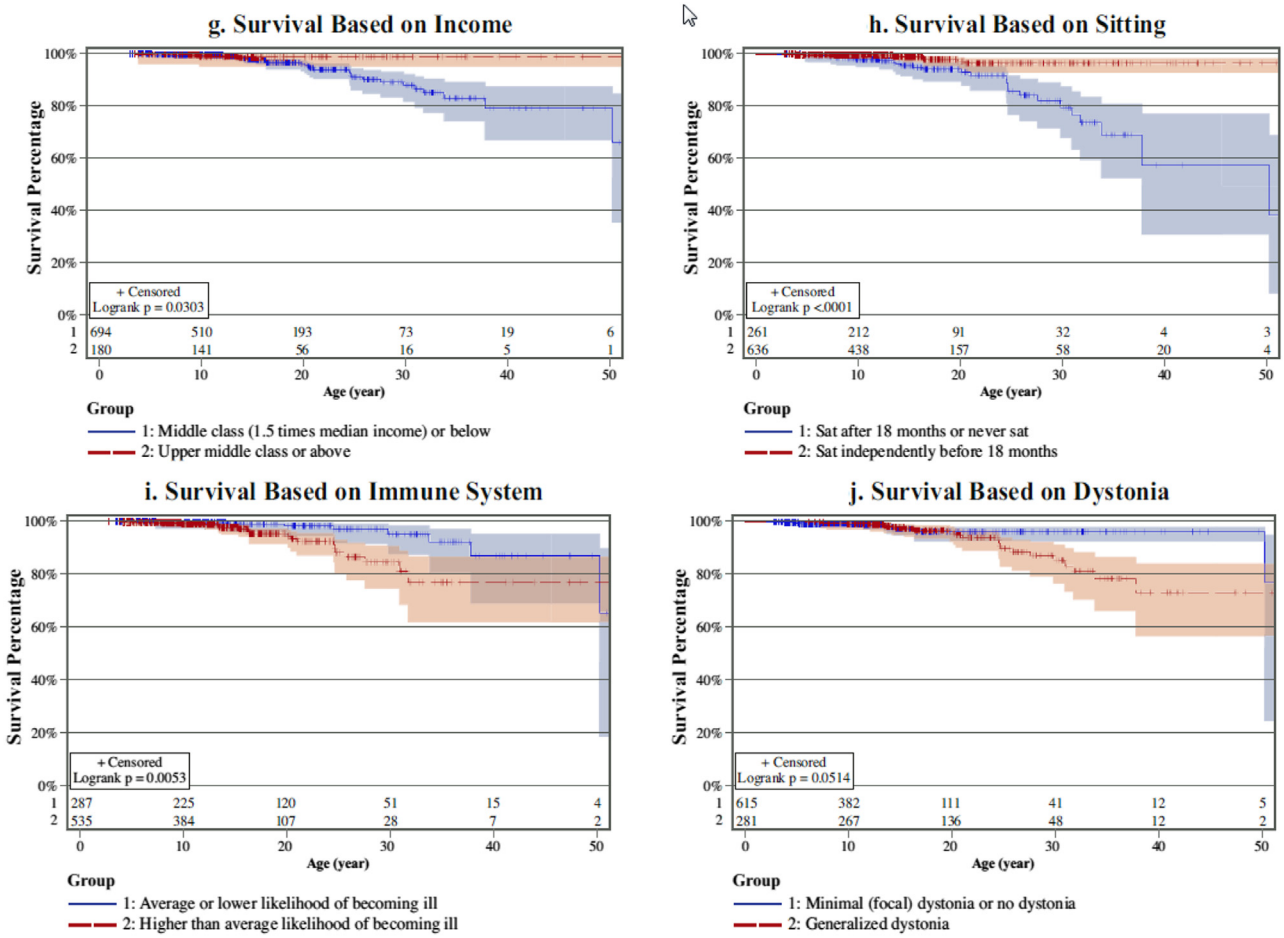

FIGURE 3. (*continued*).

separation of these groups suggested in a recent publication.[16]

Overall disease severity was strongly associated with mortality in classic RTT, and weakly associated with mortality in atypical severe RTT and DUP males. Classic RTT is a heterogeneous disorder in many respects, and the association with mortality likely reflects the presence or absence of specific phenotypic characteristics. The lack of association between mortality and severity in the other groups may be due to lower heterogeneity, perhaps because of selection bias or the absence of the effect of lyonization (in the case of males). However, the small number of participants in these groups would require a profound effect to be statistically significant.

Since severity scales in RTT are constructed based on a collection of the features and comorbidities of the disorder, we examined these in detail in classic RTT using a regression model, and found that several features were independently associated with mortality. Among these, the most profound differences in survival curves (Fig 3) were for those who were unable to stand, walk or sit independently, were low weight, had frequent hospitalizations, or had poor overall health as perceived by their caregivers. Additionally, seizure severity, dystonia, rigidity, hand use, verbal language and microcephaly were independently associated with mortality. Many of the features associated with mortality are treatable or preventable conditions. Early and constant implementation of therapy can maintain ambulation and may maintain hand use and some verbal language.[23] Moreover, aggressive nutrition and gastrostomy placement results in improved weight.[31] Therefore, these results suggest specific features for physicians and therapists to target that could result in improved survival in RTT. Notably, degree of parental concern about health or mortality was not associated with death.

This is also the first natural history study to report survival in *MECP2* duplication syndrome, and adds to the small body of work on males with *MECP2* mutations.[32] The clinical phenotype of these disorders is substantially different from that of RTT, and, not surprisingly, survival is quite different from classic RTT. Although DUP can result in frequent infections, and one review suggests a high rate of early mortality, only 2 of the 28 male DUP participants in our study died, both of unknown causes, and others were followed into their third decade. Death was more common in non-RTT males, occurring in 6 of the 20 recruited, with death before age 10 in 3 of these. Again, cause of death was often unknown, but was presumed to be cardiorespiratory in most.

Neither our cohort nor the Australian cohort demonstrated a significant association between mutation type and

mortality. Although participants with large deletions had the highest proportion of mortality in our study and the Australian study, neither reached statistical significance. Moreover, the R294X mutation had the second highest mortality rate in our study, but conferred a nonsignificant protective effect in the Australian cohort. While one study suggested that R270X is associated with early death, other longitudinal studies have found that individuals with R270X can survive into their fifth decade.[23,33,34] These inconsistencies support the notion that the association between genotype and survival, if any exists, is weak. Nonetheless, the common finding of higher mortality in the large deletion group bears further examination.

Estimates of longevity in all longitudinal studies of RTT to date, including our study, are subject to survival bias. However, our large cohort and long follow-up period, overlapping several decades, resulted in a narrow confidence interval for classic RTT up to age 50 years. We can estimate, with 95% confidence, that at least 95% of the classic RTT population survive until age 20, 80% survive until age 35, and more than 70% survive until age 50. In contrast, in the Australian cohort, only 77.6% survived until 20 years and 59.8% survived until 37 years. Several differences between these studies bear examination. In the Australian cohort, only 18% walked independently. We found that walking, even with assistance, was associated with improved survival, and this could suggest either a selection bias in our study, or that aggressive physical therapy in the United States has resulted in improved ambulation. Additionally, only 71% of those older than age 18 in the Australian cohort were living at home, in contrast with the 91% older than 18 years old living at home in our cohort. This may suggest that caregivers of individuals in institutions were less likely to travel to participate in our natural history study.

When examined individually, lower height, weight, and head circumference, but not low body mass index, were associated with a higher proportion of mortality. This is likely because body mass index is a ratio of height and weight, and does not reflect severity in those with both low weight and height. Additionally, because the majority of RTT patients are below the lower cutoffs for weight and height on normative references, the RTT-specific references were more sensitive to the association with mortality. Low weight and microcephaly were the only anthropometric variables that were significant in the regression model. Because weight is modifiable, targeting this aggressively with early supplementation, via gastrostomy tube if necessary, may improve longevity. However, this strategy is only likely to benefit those who are malnourished, not those who are small due to nonmodifiable disease factors.

Conclusion

Longevity is a major concern of families after receiving the diagnosis of RTT. These data help with anticipatory guidance for families, which we believe should be addressed soon after the diagnosis is made to allay unspoken concerns. Because patients may outlive their caregivers, the issue of long-term planning needs to be addressed as children age. Additionally, the natural history data reveal associations with growth, epilepsy, and ambulation, all of which can be addressed with appropriate routine management.

The Angelman, Rett, Prader-Willi syndrome consortium (U54HD61222) is part of the Rare Diseases Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Science (NCATS). This consortium is funded through collaboration between NCATS, and the Eunice Kennedy Shriver Child Health and Human Development Institute (grant number: HD06122). This research was also supported by the International Rett Syndrome Foundation, the Civitan International Research Center, and NIH RR019478. The authors report no conflicts of interest. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors thank Eric Pedrotty for statistical analysis of socioeconomic data. The authors acknowledge the gracious participation and provision of information by the families of the reported participants. Dr. Mary Lou Oster-Granite, Health Scientist Administrator at NICHD, provided invaluable guidance, support, and encouragement for this Rare Disease initiative.

References

1. Fehr S, Bebbington A, Nassar N, et al. Trends in the diagnosis of Rett syndrome in Australia. *Pediatr Res*. 2011;70:313-319.
2. Naidu S, Murphy M, Moser HW, Rett A, Opitz JM, Reynolds JF. Rett syndrome - natural history in 70 cases. *Am J Med Genet*. 1986;25:61-72.
3. Armstrong D, Dunn JK, Antalffy B, Trivedi R. Selective dendritic alterations in the cortex of Rett syndrome. *J Neuropathol Exp Neurol*. 1995;54:195-201.
4. Neul JL, Zoghbi HY. Rett syndrome: a prototypical neurodevelopmental disorder. *Neuroscientist*. 2004;10:118-128.
5. Kirby RS, Lane JB, Childers J, et al. Longevity in Rett syndrome: analysis of the North American Database. *J Pediatr*. 2010;156:135-138.e131.
6. Tarquinio DC, Motil KJ, Hou W, et al. Growth failure and outcome in Rett syndrome: specific growth references. *Neurology*. 2012;79:1653-1661.
7. Leonard H, Ravikumara M, Baikie G, et al. Assessment and Management of Nutrition and Growth in Rett Syndrome. *J Pediatr Gastroenterol Nutr*. 2013;57:451-460.
8. Percy AK, Lee HS, Neul JL, et al. Profiling scoliosis in Rett syndrome. *Pediatr Res*. 2010;67:435-439.
9. Glaze DG, Percy AK, Skinner S, et al. Epilepsy and the natural history of Rett syndrome. *Neurology*. 2010;74:909-912.
10. Motil KJ, Caeg E, Barrish JO, et al. Gastrointestinal and nutritional problems occur frequently throughout life in girls and women with Rett syndrome. *J Pediatr Gastroenterol Nutr*. 2012;55:292-298.
11. Kerr AM, Armstrong DD, Prescott RJ, Doyle D, Kearney DL. Rett syndrome: analysis of deaths in the British survey. *Eur Child Adolesc Psychiatry*. 1997;6(Suppl 1):71-74.
12. Freilinger M, Bebbington A, Lanator I, et al. Survival with Rett syndrome: comparing Rett's original sample with data from the Australian Rett Syndrome Database. *Dev Med Child Neurol*. 2010;52:962-965.
13. Anderson A, Wong K, Jacoby P, Downs J, Leonard H. Twenty years of surveillance in Rett syndrome: what does this tell us? *Orphanet J Rare Dis*. 2014;9:87.
14. Hagberg B, Hanefeld F, Percy A, Skjeldal O. An update on clinically applicable diagnostic criteria in Rett syndrome. Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European Paediatric Neurology Society Meeting, Baden Baden, Germany, 11 September 2001. *Eur J Paediatr Neurol*. 2002;6:293-297.
15. Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol*. 2010;68:944-950.
16. Neul JL, Lane JB, Lee HS, et al. Developmental delay in Rett syndrome: data from the natural history study. *J Neurodev Disord*. 2014;6:20.
17. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data* 2000;(314):1-27.
18. Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Stat Med*. 1998;17:407-429.

19. Cuddapah VA, Pillai RB, Shekar KV, et al. Methyl-CpG-binding protein 2 (MECP2) mutation type is associated with disease severity in Rett syndrome. *J Med Genet*. 2014;51:152-158.
20. *IBM SPSS Statistics for Windows [computer program]. Version 22.0*. Armonk, NY: IBM Corp; 2013.
21. Ellaway CJ, Sholler G, Leonard H, Christodoulou J. Prolonged QT interval in Rett syndrome. *Arch Dis Child*. 1999;80:470-472.
22. Nielsen JB, Ravn K, Schwartz M. A 77-year-old woman and a preserved speech variant among the Danish Rett patients with mutations in MECP2. *Brain Dev*. 2001;23(Suppl 1):S230-S232.
23. Lotan M, Merrick J, Kandel I, Morad M. Aging in persons with Rett syndrome: an updated review. *ScientificWorldJournal*. 2010;10:778-787.
24. Jacobsen K, Viken A, von Tetzchner S. Rett syndrome and ageing: a case study. *Disabil Rehabil*. 2001;23:160-166.
25. Halbach NS, Smeets EE, Schrander-Stumpel CT, van Schrojenstein Lantman de Valk HH, Maaskant MA, Curfs LM. Aging in people with specific genetic syndromes: Rett syndrome. *Am J Med Genet A*. 2008;146A:1925-1932.
26. Vignoli A, La Briola F, Peron A, et al. Medical care of adolescents and women with Rett syndrome: an Italian study. *Am J Med Genet A*. 2012;158A:13-18.
27. Halbach NS, Smeets EE, Steinbusch C, Maaskant MA, van Waardenburg D, Curfs LM. Aging in Rett syndrome: a longitudinal study. *Clin Genet*. 2013;84:223-229.
28. Sarajlija A, Kisic-Tepavcevic D, Nikolic Z, et al. Epidemiology of rett syndrome in serbia: prevalence, incidence and survival. *Neuroepidemiology*. 2015;44:1-5.
29. Leonard H, Bower C, English D. The prevalence and incidence of Rett syndrome in Australia. *Eur Child Adolesc Psychiatry*. 1997;6(Suppl 1):8-10.
30. Bienvenu T, Philippe C, De Roux N, et al. The incidence of Rett syndrome in France. *Pediatr Neurol*. 2006;34:372-375.
31. Motil KJ, Morrissey M, Caeg E, Barrish JO, Glaze DG. Gastrostomy placement improves height and weight gain in girls with Rett syndrome. *J Pediatr Gastroenterol Nutr*. 2009;49:237-242.
32. Villard L. MECP2 mutations in males. *J Med Genet*. 2007;44:417-423.
33. Hagberg B. Rett syndrome: long-term clinical follow-up experiences over four decades. *J Child Neurol*. 2005;20:722-727.
34. Jian L, Archer HL, Ravine D, et al. p.R270X MECP2 mutation and mortality in Rett syndrome. *Eur J Hum Genet*. 2005;13:1235-1238.

People are lonely because they build walls instead of bridges.

Joseph Fort Newton