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Original Article

Age of Diagnosis in Rett Syndrome: Patterns of Recognition Among Diagnosticians and Risk Factors for Late Diagnosis

Daniel C. Tarquinio DO, MS-CI [a,*], Wei Hou PhD [b], Jeffrey L. Neul MD, PhD [c], Jane B. Lane BSN, RN [d], Katherine V. Barnes BSc [e], Heather M. O'Leary BSc [e], Natalie M. Bruck BSc [e], Walter E. Kaufmann MD, PhD [e], Kathleen J. Motil MD, PhD [f], Daniel G. Glaze MD [f], Steven A. Skinner MD [g], Fran Annese LMSW [g], Lauren Baggett MS, CGC [g], Judy O. Barrish BSN, RN [f], Suzanne P. Geerts MS, RD [d], Alan K. Percy MD [d]

[a] *Children's Healthcare of Atlanta, Emory University, Atlanta, Georgia*
[b] *Stony Brook University Medical Center, Stony Brook, New York*
[c] *Rady Children's Hospital, University of California, San Diego, California*
[d] *University of Alabama at Birmingham, Alabama*
[e] *Boston Children's Hospital, Boston, Massachusetts*
[f] *Baylor College of Medicine, Houston, Texas*
[g] *Greenwood Genetic Center, Greenwood, South Carolina*

ABSTRACT

PURPOSE: Diagnosis of Rett syndrome (RTT) is often delayed. We sought to determine the type of physician who typically makes the RTT diagnosis and to identify risk factors for delayed diagnosis. **METHODS:** A total of 1085 participants from the multicenter longitudinal RTT natural history study with classic and atypical RTT were recruited between 2006 and 2014. Age of diagnosis, diagnostician, diagnostic criteria, and clinical and developmental data were collected. **RESULTS:** Among 919 classic and 166 atypical RTT participants, the median diagnosis age was 2.7 years (interquartile range 2.0-4.1) in classic and 3.8 years (interquartile range 2.3-6.9) in atypical RTT. Pediatricians made the diagnosis of classic RTT rarely (5.2%); however, the proportion diagnosed by pediatricians has increased since 2006. Since the first diagnostic criteria, the age of diagnosis decreased among subspecialists but not pediatricians. Odds of a pediatrician making the diagnosis of classic RTT were higher if a child stopped responding to parental interaction, and lower if they possessed gastroesophageal reflux, specific stereotypies, lost babbling, or the ability to follow commands. Delayed acquisition of basic gross motor skills or finger feeding was associated with younger diagnosis; delayed acquisition of higher level fine motor skills, later onset of supportive features, and normal head circumference were associated with late diagnosis. Thirty-three percent with microcephaly before 2.5 years were diagnosed after the median age of 2.7 years. **CONCLUSIONS:** Age of RTT diagnosis has improved among subspecialists, and pediatricians have made the diagnosis of classic RTT more frequently since 2006. Strategies for educating diagnosticians should incorporate specific risk factors for delayed diagnosis.

Keywords: Rett syndrome, *MECP2*, early diagnosis, risk factors, prognosis

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DCT participated in study conduct, data collection, manuscript preparation, performed statistical analyses, and approved the final manuscript as submitted. WH performed statistical analyses, participated in manuscript preparation, and approved the final manuscript as submitted. JLN, JBL, AKP, JLN, JBL, and AKP participated in study conceptualization, study conduct, data collection, manuscript review, and approved the final manuscript as submitted. KVB, HMO, WEK, KJM, DGG, SAS, FA, LB, JOB, SPG, NMB, WEK, KJM, and DGG participated in study conduct, data collection, manuscript review, and approved the final manuscript as submitted.

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* Communications should be addressed to: Dr. Tarquinio; Division of Child Neurology; Rett Syndrome Clinic Director; Assistant Professor; Emory University; 1605 Chantilly Drive NE; Suite 300; Atlanta, GA 30324.
E-mail address: Daniel.tarquinio@emory.edu

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Introduction

Rett syndrome (RTT), the leading cause of profound intellectual disability in females, is characterized by apparently normal early development followed by psychomotor regression. Despite association with mutations in the *MECP2* gene in the majority of patients, the diagnosis of RTT remains clinical.[1] Regression and midline hand stereotypies typically commence between 12 and 24 months, but can begin after 4 years.[2] Moreover, nonspecific developmental abnormalities can be present before 6 months.[3] Mutation type, associated with age of onset of regression and hand stereotypies, accounts for some variability in age of presentation.[4,5]

Reports on average age of diagnosis are limited; age of diagnosis in Australia decreased from a mean of 10.1 years for those born before 1980 to 2.5 years for those born between 2004 and 2006, possibly because of updates to RTT diagnostic criteria and the introduction of genetic testing.[6] RTT presents with a broad range of features, and 2-4 years may pass between initial presentation and diagnosis.[7] In Australia, delayed diagnosis has been associated with year of birth,[6] late or atypical presenting features,[7] and onset of developmental milestones and stereotypies.[8] However, no US study has examined risk factors for delayed diagnosis—whether pediatricians or subspecialists typically make the diagnosis—or the impact of developmental screening strategies on age of RTT diagnosis.

Early identification of developmental disorders is an important role of pediatricians[9]; they are the gatekeepers to further access to services. Data on age of diagnosis and factors associated with delayed diagnosis could raise awareness about the presentation of RTT. The American Academy of Pediatrics has recommended developmental surveillance and screening beginning at 9 months of age,[9] which raises two questions. Are children with RTT, who typically present with both developmental delay and regression, being detected by pediatricians? If so, do specific characteristics guide pediatricians to diagnose?

To improve appreciation of the clinical presentation of RTT and recognition of specific features among US health care providers, we examined the age of diagnosis and associated factors in a large US cohort. The aims of this study were two-fold: (1) to investigate the influence of clinical, demographic, and socioeconomic features as well as changes in diagnostic criteria on age of diagnosis and (2) to determine what type of physician made the initial diagnosis. We hypothesized that specific clinical features and patterns of development are associated with age of diagnosis and what type of physician makes the diagnosis. We also explored the influence of genetic testing and revision of developmental screening strategies on age of diagnosis.

Methods

Study design and participants

Participants were recruited, as described previously,[10] from 2006 to 2014 through the multicenter RTT natural history study (RNHS) at one of eight US sites and evaluated every 6 months until age 6 and every 12 months thereafter. All participants had *MECP2* testing. An RNHS neurologist or geneticist characterized diagnosis based on consensus criteria.[1,11] Participants with clinical classic or atypical RTT were analyzed, regardless of *MECP2* results, but those with other mutations were excluded; summary data were collected for males, those with *MECP2* duplication, and those with *MECP2* mutation who did not fulfill clinical criteria for RTT (non-RTT).

The age of RTT diagnosis and developmental history were obtained using a combination of family or caregiver reports, baby books, photos or videos, *MECP2* testing dates, and clinician notes. If the age of diagnosis was not available, a surrogate was based on *MECP2* testing date, and the requesting physician was credited with the diagnosis. Demographic data included race and ethnicity, type of residence, and parental age. Median income and population density were estimated using address. At each visit, an RNHS physician completed neurological examination, an anthropometrist recorded somatic measurements, and two quantitative scales of disease severity—the motor behavioral assessment and clinical severity scale described previously[10]—were administered. Each institutional review board approved the study, and the RNHS clinician verified all data.

Data categorization

The period of diagnosis was categorized based on historical events (i.e., secular variation; Table 1).[1,9,11-17] Normative[18] and RTT-specific[10] growth Z-scores were calculated. Developmental acquisitions were categorized based on Denver-II percentile[19] as normal (<75th), concerning (75th to 90th), or delayed (>90th).

Statistical analysis

Descriptive analyses were performed. Age of diagnosis distribution is positively skewed, so nonparametric analyses were performed when possible. Kruskal-Wallis H test was used to evaluate the association between categories (e.g., diagnosis, period effect) and age of diagnosis; Mann-Whitney U tests (with Bonferroni correction) were used for post-hoc and other comparisons between two groups. Logistic regression was used to determine which Rett-related features and developmental milestones predict whether the diagnosis of classic RTT was made by a pediatrician or specialist. Nonparametric correlation (Kendall's τ_b) was used to compare continuous variables such as age of diagnosis and age of onset of RTT characteristics (with Bonferroni correction). Predictors were included in regression models if P value was <0.10, and $P < 0.05$ was

TABLE 1.
Historical Period and Age of Diagnosis by Subspecialists

Period	N	Median Age of Diagnosis (Years)	Mean Rank	Significantly Different From Periods
A: 1983*-1984	13	6.33	645.8	F‡‡, G§§, H§§, I§§
B: 1985†-1987	50	6.17	591.0	D§§, F§§, G|||, H|||, I|||
C: 1988‡-1994	84	3.08	494.6	G§§, H|||, I§§
D: 1995§-1998	64	2.91	410.3	B§§
E: 1999‖-2000	88	3.08	471.3	H§§
F: 2001¶	39	2.50	376.7	A‡‡, B§§
G: 2002#-2005	196	2.50	377.1	A§§, B|||, C§§
H: 2006**-2009	194	2.41	355.9	A§§, B|||, C|||, E§§
I: 2010††-2014	96	2.54	364.8	A§§, B|||, C§§
Total	824	2.75		

Periods divided based on the following.
* 1983, first description of the disorder in English.
† 1985, first diagnostic criteria.
‡ 1988, update to diagnostic criteria.
§ 1995, atypical RTT criteria.
‖ 1999, association between *MECP2* mutations and RTT.
¶ 2001, clinical availability of *MECP2* testing and American Academy of Pediatrics developmental screening recommendations.
# 2002, update to diagnostic criteria.
** 2006, American Academy of Pediatrics routine screening algorithm for developmental disorders.
†† 2010, update to diagnostic criteria.
‡‡ $P < 0.05$.
§§ $P < 0.01$.
\|\|\| $P < 0.001$.

considered statistically significant for all other comparisons. Nonparametric comparisons are summarized using median and interquartile range (IQR). Analyses were performed using SPSS, version 21[20]; ArcMap Editor[21]; and Address Coder Premium.[22]

Results

Among 1205 participants, 21 were excluded because of incomplete data and 2 with *CDKL5* mutation and atypical RTT were excluded. The single male with atypical RTT, 61 non-RTT and 35 duplication participants were excluded from analysis, but age of diagnosis is summarized in eTable 1 (supplementary material). Median age of diagnosis was 5.4 years for non-RTT females, 3.5 years for non-RTT males, 37.8 years for duplication females, and 7.3 years for duplication males. Remaining female participants (919 classic RTT and 166 atypical RTT) were followed for up to 8.2 years (median 4.0 years). Birth year ranged from 1943 to 2012 (median 2001), and participants were between 8 months and 66.5 years old at enrollment (median 6.8 years). Demographics are summarized in eTable 2; participants were mostly Caucasian, non-Hispanic (supplementary material).

Characteristics of diagnosis

Distribution

Participants were diagnosed between 1983 and 2013. Age of diagnosis ranged from 7 months to 53.0 years. Median age of diagnosis was 2.7 years (IQR 2.0-4.1) in classic and 3.8 years (IQR 2.3-6.9) in atypical RTT (Table 2).

Who made the diagnosis

Diagnosis was typically made by a neurologist, developmental pediatrician, or geneticist, and infrequently by a primary care provider (Table 2). Odds of a pediatrician diagnosing classic RTT were lower than specialists if the child had lost babbling or the ability to follow commands with a gesture, or if gastroesophageal reflux was present (Table 3). Additionally, pediatricians were less likely to diagnose classic RTT if clasping, posturing, clapping, or tapping stereotypies were present before diagnosis, but equally likely to diagnose if common stereotypies (hand wringing) were present. Odds of a pediatrician making the diagnosis were higher if the child had lost the ability to be consoled by being held or had stopped reacting to the parents' voice or the command "no." Insufficient atypical participants existed for logistic regression. The age of diagnosis was similar among all diagnosticians for both classic ($\chi^2(6) = 11.02$, $P = 0.09$) and atypical RTT ($\chi^2(6) = 12.28$, $P = 0.06$).

Secular period

Proportion of pediatricians making the diagnosis of classic RTT was similar in all periods before 2006 (4.1%), but increased after 2006 (8.2%, $P = 0.02$). Pediatricians diagnosed atypical RTT in 2.4% of cases, which did not change with time period. Median age of diagnosis of classic RTT by subspecialists varied with time period ($\chi^2(8) = 76.10$, $P < 0.001$, Figure); age of diagnosis declined after 1987, with stabilization after 2000, and no significant change in age of diagnosis from 2001 to the present (Table 1). Median age of diagnosis did not change for classic RTT diagnosed by a pediatrician or for atypical RTT regardless of diagnostician (data not shown).

Ages of diagnosis differed for subspecialists based on period, demonstrating a decline in age of diagnosis with stabilization after 2000. No significant trend was present for pediatricians. *Post-hoc* comparisons are detailed in Table 1. Box-plots indicate median age and IQR, and whiskers

TABLE 2.
Diagnostician and Age of Diagnosis

Diagnostician	Number	Percent	Median Age (Years)	Interquartile Range	Minimum Age	Maximum Age	Mean Rank*,†
Classic Rett syndrome							
Pediatrician	48	5.2	2.4	1.8-3.5	1.2	18.1	379.4
Developmental pediatrician	273	29.7	3.0	2.0-4.2	0.6	34.1	465.0
Neurologist	324	35.3	2.7	2.0-4.4	0.8	31.0	446.0
Geneticist	204	22.2	2.5	2.0-3.5	0.9	40.0	415.6
Other specialist	23	2.5	2.8	2.1-4.5	1.5	14.8	465.8
Other primary care provider	2	0.2	NC	NC	3.1	20.0	703.8
Family member or teacher	12	1.3	3.3	2.0-13.7	1.3	53.0	530.3
Missing	16	1.7					
Overall	919	100.0	2.7	2.0-4.1	0.6	53.0	
Atypical Rett syndrome							
Pediatrician	4	2.4	5.7	1.6-35.4	1.5	44.1	84.0
Developmental pediatrician	50	30.1	5.1	2.5-8.1	1.4	37.1	90.1
Neurologist	55	33.1	3.5	2.4-6.1	1.0	30.8	76.5
Geneticist	44	26.5	2.9	2.1-5.1	0.7	27.0	67.2
Other specialist	3	1.8	7.0	NC	5.3	10.0	120.8
Other primary care provider	1	0.6	25.8	NC	NC	NC	154.0
Family member or teacher	1	0.6	8.0	NC	NC	NC	128.0
Missing	8	4.8					
Overall	166	100.0	3.8	2.3-6.9	0.7	44.0	

Abbreviation:
NC = Not calculated
* $P = 0.10$.
† $P = 0.06$.

TABLE 3.
Odds of a Pediatrician Making the Diagnosis of Classic RTT Based on Specific Characteristics

Characteristic	Odds Ratio	*P* Value	95% CI
Regression			
Loss of ability to quiet to parent's voice	2.5	0.009	1.3-5.0
Loss of ability to inhibit to "no"	3.8	0.001	1.8-8.1
Loss of affinity for being held	3.1	0.001	1.6-5.9
Loss of babbling	0.6	0.09	0.3-1.1
Loss of ability to follow a command with a gesture	0.4	0.04	0.1-0.9
Hand stereotypies			
Clapping or rapping	0.3	0.01	0.1-0.8
Clasping or posturing	0.2	0.07	0.1-1.3
Supportive features			
Gastroesophageal reflux	0.6	0.06	0.3-1.0

Abbreviations:
CI = Confidence interval
RTT = Rett syndrome
Nonsignificant predictor variables from regression are not shown.

extend 1.5× the IQR. Ovals indicate outliers, and diamonds indicate extreme outliers.

Clinical characteristics

Age at diagnosis of classic RTT was younger in children with delayed acquisition of pulling to stand, supported walking, independent walking, or finger feeding, but older in children with delayed acquisition of pincer grasp or transfer of objects from hand to hand (Table 4). Age of onset of the following characteristics was correlated with age of diagnosis: hyperventilation (r_τ [380] = .21), breath-holding (r_τ [470] = .25), air swallowing (r_τ [318] = .25), drooling (r_τ [528] = .20), bruxism (r_τ [694] = .29), constipation (r_τ [580] = .25), gastroesophageal reflux (r_τ [432] = .26), bone fractures (r_τ [136] = .27), stereotypies (r_τ [851] = .30), self-abuse (r_τ [428] = .24), scoliosis (r_τ [300] = .23), developmental regression (r_τ [874] = .21), and head circumference deceleration (r_τ [668] = .11, all $P < 0.001$). Neither child's nor parents' quality of life was associated with age at diagnosis (data not shown).

Growth

Rett-specific height z-score (r_τ [296] = .12, $P = 0.04$) and head circumference z-score (r_τ [287] = .19, $P = 0.001$) at time of diagnosis were higher in those diagnosed at an older age. However, of the 16% (39/247) who exhibited acquired microcephaly (below the second percentile) before 2.5 years, 33.3% (13/39) were not diagnosed until after the median age of 2.7 years and 46% (6/13) of these were not diagnosed until after the upper quartile of 4.1 years. Of the 83% (682/824) who eventually exhibited microcephaly, 19% (128/682) were not diagnosed until after 4.1 years.

Developmental delay, supportive features, and diagnosis of classic RTT

Because age of milestone and supportive feature acquisition were not recorded on all participants, hypothesis testing could not be performed; however, the average time from appearance of a characteristic to diagnosis is instructive. Most participants exhibited stereotypies and language regression prior to diagnosis (Table 5); stereotypies had been occurring for a median of 1.1 years (IQR 0.5-2.5 years, n = 685). The longest time from regression to diagnosis was

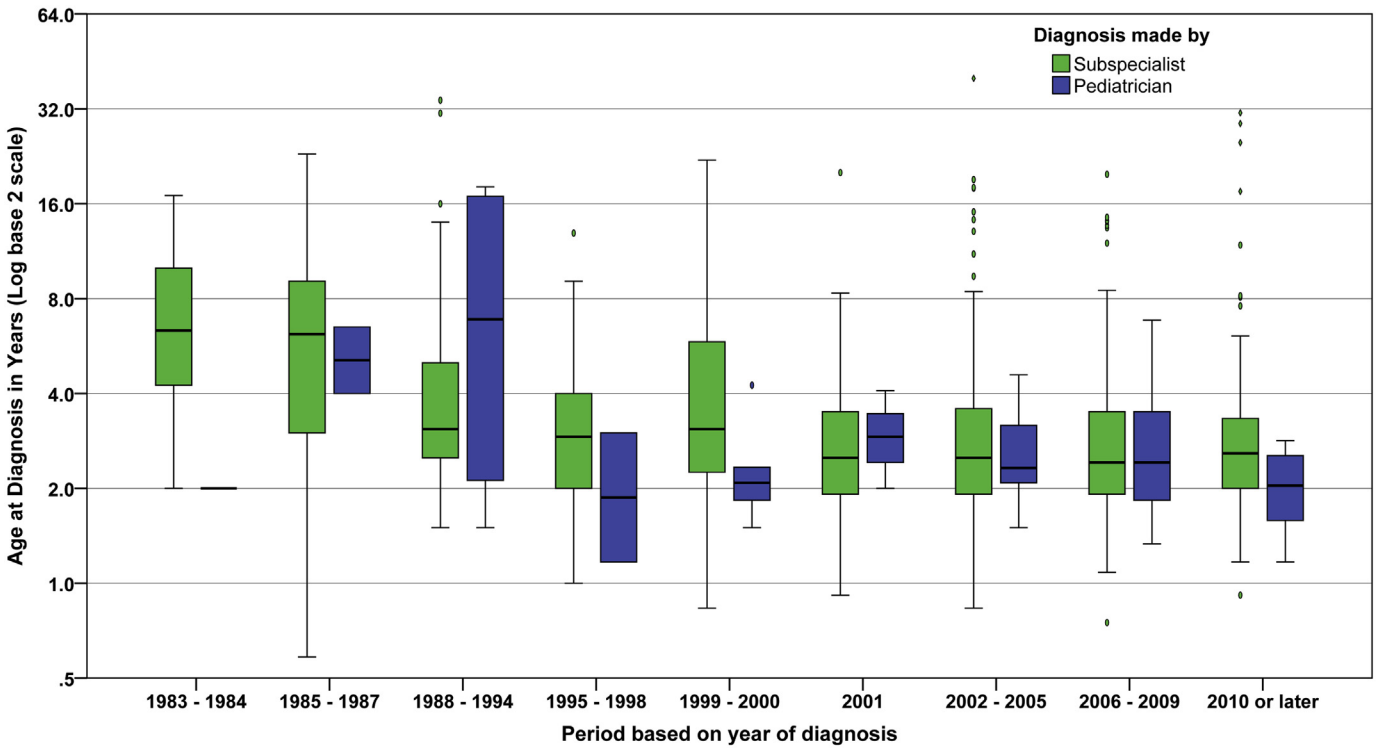

FIGURE.
Age of classic Rett syndrome diagnosis and diagnostician, based on historical period. (The color version of this figure is available in the online edition.)

TABLE 4.
Age of Diagnosis of Classic RTT Among All Diagnosticians in the Presence of Normal, Concerning, or Delayed Acquisition of Developmental Milestones

Developmental Milestone	Median Age of Diagnosis and Developmental Milestones			*P* Value
	Normal (IQR, n)	Concerning (IQR, n)	Delayed (IQR, n)	
Pulling to stand	3.6 (2.5-6.9, 109)	2.8 (2.1-4.3, 311)	2.6 (2.0-4.0, 89)	0.01
Walking with support	3.8 (2.3-6.5, 152)	2.8 (2.1-4.0, 355)	2.5 (2.0-4.0, 117)	<0.001
Independent walking	9.0 (3.1-9.0, 3)	3.5 (2.4-5.4, 309)	2.9 (2.2-4.1, 160)	0.04
Finger feeding	3.6 (2.5-6.9, 109)	2.8 (2.1-4.3, 311)	2.6 (2.0-4.0, 89)	0.02
Transfer from hand to hand	2.5 (1.9-3.5, 387)	2.1 (1.5-2.8, 26)	3.3 (2.6-4.8, 42)	0.002
Pincer grasp	2.5 (2.0-3.5, 306)	2.7 (2.1-4.1, 132)	3.6 (2.2-6.0, 56)	0.008

Abbreviations:
IQR = Interquartile range
RTT = Rett syndrome
Median age in years (IQR, n). *P*-value adjusted for multiple comparisons using Bonferroni correction.

for advanced skills: a median of 6.3 years after losing the ability to pedal a tricycle (IQR 1.7-9.6 years, n = 12), 1.7 years after losing phrases (IQR 0.6-4.7 years, n = 125), and 1.6 years after losing independent walking (IQR 0.4 3.8 years, n = 103). Time to diagnosis was shortest after loss of more fundamental skills: a median of 0.8 years after loss of finger feeding (IQR 0.3-1.6 years, n = 334), holding a bottle (IQR 0.3-2.0 years, n = 269), transferring objects from hand to hand (IQR 0.3-1.6 years, n = 287), and pulling to stand (IQR 0.4-2.6 years, n = 112), and a median of 0.9 years after loss of pincer grasp (IQR 0.3-2.0 years, n = 340) and reaching (IQR 0.4-2.1 years, n = 328). The longest median intervals after appearance of supportive features were for gallbladder dysfunction (3.3 years, IQR 1.7-10.0 years, n = 5), scoliosis (1.8 years, IQR 0.4-4.6 years, n = 76), self-abusive behaviors (1.8 years, IQR 0.6-3.8 years, n = 55), gastroesophageal reflux (1.7 years, IQR 1.0-2.9 years, n = 257), and bone fracture (1.6 years, IQR 1.0-4.5, n = 54), and the shortest median time was after appearance of finger-rubbing stereotypies (0.7 years, IQR 0.3-2.0 years, n = 111), hyperventilation (0.9 years, IQR 0.3-2.9 years, n = 207), breath-holding (1.0 years, IQR 0.3-2.2 years, n = 259), or bruxism (1.0 years, IQR 0.5-2.1 years, n = 478).

TABLE 5.
Characteristics Present by History Prior to Diagnosis With Classic RTT (n = 869*)

Characteristic	Specific regression	Percent
Core features		
Stereotypies		86.4
Fine motor regression	Overall	77.0
	Holding bottle	32.2
	Pincer grasp	40.8
	Finger feeding	40.1
Language regression	Overall	87.3
	Babbling	37.9
	Single word with meaning	58.7
	Phrases	14.5
	Follow command with gesture	16.2
	Follow command without gesture	10.5
Other regression		
Gross motor regression†	Overall	55.7
	Pull to sit	9.0
	Crawling	16.6
	Walk independently	4.8
Loss of attention	Visual	22.8
	Auditory	19.8
Supportive features		
Bruxism		56.7
Constipation		43.4
Self-abusive		41.5
Drooling		39.2
Breath-holding		30.7
Gastroesophageal reflux		30.6
Hyperventilation		24.6
Aerophagia		22.2
Scoliosis		8.9
Bone fractures		6.3
Gallbladder dysfunction		0.6

Abbreviation:
RTT = Rett syndrome
* 50 participants had incomplete data on development and supportive features.
† Gait apraxia (a core diagnostic feature) could not be evaluated retrospectively; therefore, gross motor regression is reported.

Demographic and socioeconomic factors

Diagnosis was made at a younger age in classic RTT if either mother (r_τ [704] = −.117, $P < 0.001$) or father (r_τ [688] = −0.104, $P < 0.001$) was older at participant's birth, and at a younger age in atypical RTT if mother was older (r_τ [111] = −.141, $P = 0.024$). Participants with an estimated household income above the national median were diagnosed earlier (median 2.5 years, IQR 2.0-4.0 years, n = 522) than those with lower income (median 3.0 years, IQR 2.1-4.6 years, n = 331, $U = 76{,}748$, $P = 0.006$). No influences of race, ethnicity, or population density on age of diagnosis were found.

Discussion

Early diagnosis in RTT offers many benefits. In addition to the opportunity for specific counseling about prognosis and potential comorbidities, many therapeutic strategies have proven effective in RTT, including physical, occupational,[23] behavioral,[24] and music therapy.[25] Guidelines for tailored programs exist[26] and can maximize therapeutic effect.[27] Gastrointestinal issues occur early in the disorder, are associated with malnutrition and growth failure,[28] and are improved by early and aggressive treatment.[29] Moreover, the effects of *MECP2* mutation on synaptic development are most evident before 2 years of age,[30] and targeted treatment options should be administered as early as possible.

In this study, age of diagnosis was associated with clinical, demographic, socioeconomic, and secular factors. Age of classic RTT diagnosis decreased after 2001, possibly from

enhanced developmental screening and widespread implementation of *MECP2* testing. Developmental delay, particularly in the motor domain, was associated with earlier diagnosis. However, children who developed and then lost more advanced skills were diagnosed later, as were those with unusual stereotypic hand movements. As in the Australian cohort,[7] we found that the age of onset of supportive features was associated with age of diagnosis. Those with less specific features, such as scoliosis, gastroesophageal reflux, bone fractures, and self-abusive behaviors, often exhibited these features for several years before diagnosis. The children of older parents were diagnosed at a younger age, perhaps because experienced parents raised concerns about their children sooner. Although population density was not a factor, higher income was associated with earlier diagnosis. Children with normal head size were typically diagnosed later, perhaps because of the myth that children must have head circumference deceleration to receive the diagnosis; in fact, a substantial proportion does not.[10] Alternately, 33% of children with early microcephaly were diagnosed after the median age of diagnosis. Therefore, the message about head circumference is two-fold: (1) early acquired microcephaly often goes unrecognized or does not lead to suspicion of RTT and (2) diagnosis should not be postponed because of the absence of microcephaly.

Although pediatricians diagnosed RTT in a minority of cases, the proportion of pediatricians making the diagnosis has increased since 2006. This increase coincides with publication of the American Academy of Pediatrics algorithm for developmental surveillance and screening, which focuses on children younger than age 2 years.[9] In general, pediatricians were more likely to diagnose RTT if the child lost the ability to be soothed by their parent or respond to simple commands. Pediatricians were less likely to make the diagnosis when the ability to follow complex commands was lost or when unusual stereotypies were present. Awareness about the complex nature of both stereotypic behaviors and regression in RTT may improve the likelihood that pediatricians will recognize RTT, refer to community-based resources, and consider sending genetic testing. Pediatricians may elect to refer to a subspecialist before suggesting the diagnosis; however, because *MECP2* mutations are highly sensitive (although not specific) for RTT, the findings presented previously may prompt genetic testing before referral.

In RTT, children appear developmentally normal during the first 6-18 months of life.[2] Most children experience early milestones later than normal[3] and regression occurs after 12 months in more than 90%. Therefore children are at risk for late diagnosis because of the "wait-and-see" approach. Delayed diagnosis has been associated with numerous factors, including age of onset of stereotypies, the absence of regression of hand use or verbal language,[7] *MECP2* mutation type, impaired acquisition of developmental milestones,[8] and year of birth.[6] In our study, many characteristic features of RTT, including the pathognomonic midline hand stereotypies,[31] were present for more than a year before diagnosis; the diagnosis was often suggested before all criteria were met. Referral and testing based on early features could lead to earlier diagnosis of "probable" RTT[1] and targeted treatment during, or even before, the period of regression.

In other disorders, age of diagnosis is associated with similar factors. Both socioeconomic factors[32] and abnormal development[33] influence age of diagnosis in autism spectrum disorders. Additionally, those with autism spectrum disorders who would most benefit from therapy are diagnosed later.[33] Year of birth[34] and number of co-occurring conditions predict age of diagnosis in fragile X syndrome,[35] and parents often raise concerns about development more than a year before diagnosis.[36] Although routine developmental screening in pediatric clinics[9] has led to earlier recognition of developmental delay in fragile X syndrome, the age of diagnosis has *not* changed since 2001 because of the "wait-and-see" approach.[35] Genotype and clinical features predict age of diagnosis in neurofibromatosis 2,[37] and clinical features and recent year of birth predict earlier diagnosis in Turner syndrome.[38] Both are disorders in which timely diagnosis has implications for management. The benefits of early diagnosis include the opportunity for genetic counseling, family planning, decreased psychosocial stress, both increased access to and earlier entry into intervention services, and greater impetus to participate in intervention programs.

Our study has some limitations, including lack of robust socioeconomic data. We compensated by using estimated measures derived from US census data. Data collection through parental recall could be considered a drawback. However, strong efforts were made to corroborate both diagnosis and age of diagnosis through detailed initial history, complete documentation of *MECP2* testing, and thorough review of clinician notes. Evaluation by a clinician facilitated both collection of retrospective data and comparison with objective clinical features on examination. Moreover, the diagnostic criteria were applied directly by one of the RNHS clinicians.

Conclusion

In this era of emerging targeted therapeutics, early diagnosis is critical. Both recognition by pediatricians and time to diagnosis among subspecialists have improved. However, no systematic effort exists to improve age of diagnosis in Rett syndrome, and median age of recognition among pediatricians has remained stable. The role of pediatricians to recognize early, subtle delay or regression cannot be overemphasized. Diagnosticians successfully recognize most stereotypic behaviors and regression of fundamental skills. However, to improve age of diagnosis, physicians should maintain a high index of suspicion between ages 6 months to 3 years and recognize that concomitant somatic problems and atypical features (e.g., normal head size) can distract from the diagnosis. Greater awareness of specific risk factors for late diagnosis, which include subtle regression and delay in advanced skills, will improve age of diagnosis and care of these complex individuals.

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ETABLE 1.
Diagnostician and Age of Diagnosis of Non-RTT and *MECP2* Duplication Participants

Diagnostician	Number	Percent	Median Age (Years)	Interquartile Range	Minimum Age	Maximum Age
Non-RTT females						
Pediatrician	3	7.3	5.8	NC	4.2	5.9
Developmental pediatrician	10	24.4	6.0	2.9-15.9	1.3	17.4
Neurologist	18	43.9	5.0	2.8-16.5	1.0	51.6
Geneticist	9	22.0	3.9	3.3-27.3	1.2	30.0
Other specialist	1	2.4	6.7	NC	NC	NC
Other primary care provider	0					
Family member or teacher	0					
Overall	41	100.0	5.4	3.0-14.4	1.0	51.6
Non-RTT males						
Pediatrician	2	10.0	NC	NC	1.3	4.2
Developmental pediatrician	2	10.0	NC	NC	11.9	20.4
Neurologist	5	25.0	4.7	2.6-9.2	1.6	12.7
Geneticist	9	45.0	2.2	0.9-3.1	0.7	4.3
Other specialist	2	10.0	NC	NC	4.4	18.1
Other primary care provider	0					
Family member or teacher	0					
Missing	0					
Overall	20	100.0	3.5	1.5-5.5	0.7	20.4
MECP2 duplication females						
Pediatrician	0					
Developmental pediatrician	0					
Neurologist	3	42.9	37.1	NC	4.5	40.6
Geneticist	4	57.1	38.5	NC	1.2	64.8
Other specialist	0					
Other primary care provider	0					
Family member or teacher	0					
Missing	0					
Overall	7	100.0	37.8	3.7-46.6	1.2	64.8
MECP2 duplication males						
Pediatrician	0					
Developmental pediatrician	4	14.3	9.0	3.8-14.7	3.2	15.5
Neurologist	9	32.1	7.3	3.2-10.5	0.6	14.8
Geneticist	15	53.6	7.5	1.6-13.5	0.5	20.0
Other specialist	0					
Other primary care provider	0					
Family member or teacher	0					
Missing	0					
Overall	28	100.0	7.3	2.9-12.0	0.5	20.0

Abbreviation:
NC = Not calculated

ETABLE 2.
Demographic Characteristics of Population and Diagnostic Category (N = 1087)

	Classic		Atypical	
	(n = 919)		(n = 166)	
Ethnicity				
Neither Hispanic, Latino, or Spanish origin	783	85%	141	85%
Hispanic, Latino, or Spanish origin	136	15%	25	15%
Race				
Unknown or refused	23	3%	4	2%
American Indian	6	1%	2	1%
Asian	35	4%	4	2%
African American	43	5%	9	5%
Hawaiian or Pacific Islander	2	<1%	0	0%
White	757	82%	142	86%
Mixed race	53	6%	5	3%
Primary residence				
Home	898	98%	163	98%
Group home	18	2%	0	0%
Institution	3	<1%	3	2%
Population density				
Rural	404	48%	66	45%
Suburban	241	29%	45	30%
Urban	193	23%	37	25%
Estimated income				
Below national median	348	42%	60	41%
Middle class	340	41%	67	45%
Upper middle class	138	17%	21	14%

Data do not sum to total number of participants in all cases because of missing data.