Characterizing Patients With Rett Syndrome in the United States: A Real-World Analysis of the Rett Syndrome Natural History Study Database

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INTRODUCTION

- Rett syndrome (RTT) is a severe neurodevelopmental disorder that almost exclusively affects females[1]
- Individuals with RTT often require lifelong care due to a variety of symptoms ranging in severity, including neurological, gastrointestinal, cardiac, endocrine, and orthopedic disorders[2]
- To date, there is no cure for RTT, and until the recent approval of trofinetide in March 2023, current treatment options have been aimed at managing symptoms and supporting daily activities[1,3,4]
- With the advent of new therapy for RTT, an understanding of current real-world treatment patterns is needed to gain insight into potential unmet needs of this population

OBJECTIVE

- Provide a comprehensive overview of demographics, clinical characteristics, RTT-related outcomes, and treatment patterns of individuals with RTT in the United States

METHODS

Data Source and Study Design

- Registry data from the 5211 Natural History of Rett Syndrome & Related Disorders study (RNHS) were used
- A retrospective, longitudinal, cohort study was used
  - The index date was defined as the date of the first visit; individuals' demographics and clinical characteristics were evaluated on this date
  - The observation period spanned from the index date (exclusive) to the earliest of end of study enrollment, death, or study end; RTT-related outcomes and treatment patterns were assessed during the observation period

Study Population

- Females with classic or atypical RTT who had ≥1 follow-up visit were included in the study
- Females with a history of brain trauma before or on the index date were excluded
- All analyses were conducted in the overall study sample and stratified by:
  - Classic RTT and atypical RTT
  - Pediatric (<18 years of age on index) and adult (≥18 years of age on index)

Study Outcomes and Statistical Analysis

- Continuous characteristics were summarized using means (standard deviations [SDs]), and categorical characteristics were summarized using frequencies and proportions

RESULTS

Study Population

- Of the 455 females who met the eligibility criteria and were included in the study, 412 (90.5%) had classic RTT and 43 (9.5%) had atypical RTT; 363 (79.8%) and 92 (20.2%) were pediatric and adult individuals, respectively

Baseline Demographics and Clinical Characteristics

- The mean (SD) age at first visit was 11.8 (9.5) years among the overall RTT population; the mean (SD) age was 7.9 (4.7) years among pediatric individuals and 27.1 (8.1) years among adult individuals. The mean (SD) age of onset of motor and communication regression was 2.3 (0.8) years overall
- Most individuals were White (87.0%) and had an *MECP2* mutation (98.2%) (**Table 1**)
- Common clinical manifestations of RTT included loss of language (95.8%), hand stereotypies (92.3%), respiratory dysfunction (75.8%), sleep disturbances (75.6%), and constipation (74.5%) (**Table 1**)
- Individuals with atypical RTT had fewer clinical manifestations than individuals with classic RTT (loss of language: 60.5% vs 99.5%, hand stereotypies: 72.1% vs 94.4%, respiratory dysfunction: 44.2% vs 79.1%, sleep disturbances: 60.5% vs 77.2%, respectively) (**Table 1**)
- Relative to pediatric individuals, a higher proportion of adults had scoliosis (73.9% vs 45.7%), constipation (83.7% vs 72.2%), and epilepsy (56.5% vs 43.5%) (**Table 1**)
- The ability to sit, stand, or walk independently was less common among individuals with classic RTT (classic: 47.3–74.0%; atypical: 58.1–79.1%) (**Table 1**)

Table 1. Demographics and clinical characteristics among females with RTT, overall and stratified by RTT type and age

Characteristics[a]	Overall RTT cohort (N = 455)	Stratification by RTT type[b]		Stratification by age[c]	
		Classic RTT (N = 412)	Atypical RTT (N = 43)	Pediatric (<18 years of age) (N = 363)	Adult (≥18 years of age) (N = 92)
Observation period,[d] years, mean ± SD [median]	4.1 ± 1.0 [4]	4.1 ± 1.0 [4]	4.1 ± 1.2 [4]	4.1 ± 1.1 [4]	4.2 ± 0.8 [4]
Clinical characteristics, n (%)					
MECP2 mutation	447 (98.2)	406 (98.5)	41 (95.3)	358 (98.6)	89 (96.7)
Birth defect[e]	54 (11.9)	50 (12.1)	4 (9.3)	46 (12.7)	8 (8.7)
Pubertal status[f]					
Premenarchal	288 (63.3)	259 (62.9)	29 (67.4)	288 (79.3)	0
Postmenarchal	167 (36.7)	153 (37.1)	14 (32.6)	75 (20.7)	92 (100)
Clinical manifestations[g]					
Loss of spoken language	436 (95.8)	410 (99.5)	26 (60.5)	348 (95.9)	88 (95.7)
Hand stereotypies	420 (92.3)	389 (94.4)	31 (72.1)	339 (93.4)	81 (88.0)
Respiratory dysfunction[h]	345 (75.8)	326 (79.1)	19 (44.2)	281 (77.4)	64 (69.6)
Sleep disturbances[i]	344 (75.6)	318 (77.2)	26 (60.5)	272 (74.9)	72 (78.3)
Constipation	339 (74.5)	308 (74.8)	31 (72.1)	262 (72.2)	77 (83.7)
Feeding problems	292 (64.2)	268 (65.0)	24 (55.8)	233 (64.2)	59 (64.1)
Autonomic symptoms	274 (60.2)	248 (60.2)	26 (60.5)	216 (59.5)	58 (63.0)
Scoliosis	234 (51.4)	217 (52.7)	17 (39.5)	166 (45.7)	68 (73.9)
Gastroesophageal reflux	212 (46.6)	198 (48.1)	14 (32.6)	164 (45.2)	48 (52.2)
Epilepsy	210 (46.2)	196 (47.6)	14 (32.6)	158 (43.5)	52 (56.5)
Fractures[j]	17 (3.7)	14 (3.4)	3 (7.0)	12 (3.3)	5 (5.4)
Gall bladder dysfunction	8 (1.8)	8 (1.9)	0	3 (0.8)	5 (5.4)
Functional characteristics,[k] n (%)					
Ability to sit	339 (74.5)	305 (74.0)	34 (79.1)	277 (76.3)	62 (67.4)
Ability to stand	223 (49.0)	198 (48.1)	25 (58.1)	177 (48.8)	46 (50.0)
Ambulation[l]	220 (48.4)	195 (47.3)	25 (58.1)	173 (47.7)	47 (51.1)
Ability to communicate[m]	34 (7.5)	31 (7.5)	3 (7.0)	26 (7.2)	8 (8.7)

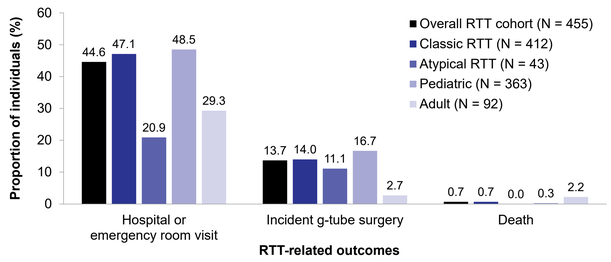
[a]Unless otherwise specified, demographics and clinical characteristics were evaluated on the date of first visit; [b]Classic or atypical diagnosis of RTT was identified at the time of study enrollment based on the latest consensus criteria for RTT; [c]Age was assessed at the date of first visit; [d]The observation period was defined as the period from the index date (exclusive) to the earliest of end of enrollment, end of data availability, or death; [e]Birth defects included encephalopathy or microcephaly; [f]Individuals who were ≥18 years of age at the date of first visit were categorized as postmenarchal. Individuals who were <18 years of age at the date of first visit but experienced (1) menarche in the year prior to the date of first visit or (2) menarche at an age younger than their age at the date of first visit were categorized as postmenarchal. All remaining individuals were categorized as premenarchal; [g]Clinical manifestations were evaluated according to individual's complete medical history up to the date of the first visit. For all clinical manifestations, excluding fractures, individuals in the RNHS data were recorded to: (1) have the respective clinical manifestation (classified as "Yes"), (2) not have the respective clinical manifestation (classified as "No"), or (3) have missing data (classified as "Missing"). For fractures, only individuals with a fracture in the year prior to the index date were recorded in the data, and, as such, individuals without a fracture could not be distinguished from individuals with missing data; [h]Respiratory dysfunction included hyperventilation, breath holding, or puffing air; [i]Sleep disturbances included having difficulty sleeping, waking at night, being hard to wake up, or day sleeping; [j]Individuals were considered as having a fracture if there was a record of a fracture occurring in the year prior to the date of first visit; [k]For all functional characteristics, individuals in the RNHS data were recorded to: (1) have the respective functional characteristic (classified as "Yes"), (2) not have the respective functional characteristic (classified as "No"), or (3) have missing data (classified as "Missing"); [l]Ambulation was defined as the ability to walk independently; [m]Individuals were classified as able to communicate if their overall communication skills were listed as normal

RNHS, Natural History of Rett Syndrome & Related Disorders study; RTT, Rett syndrome; SD, standard deviation

RTT-Related Outcomes During the Observation Period

- Median follow-up time in the overall cohort was 4 years and generally consistent across subgroups
- Nearly half (44.6%) of all individuals had a hospital or emergency room visit during follow-up
  - Larger proportions of hospital or emergency room visits were observed among individuals with classic RTT relative to atypical RTT (47.1% vs 20.9%, respectively) and among pediatric individuals relative to adults (48.5% vs 29.3%, respectively) (**Figure 1**)
- The incidence of g-tube surgeries was 13.7%, and a higher proportion of pediatric individuals had incident g-tube surgery relative to adults (16.7% vs 2.7%, respectively) (**Figure 1**)
- Mortality was rare (0.7%) in the overall population, and all observed deaths were due to natural causes, with no specific natural cause documented (**Figure 1**)

Figure 1. RTT-related outcomes[a,b] among females with RTT, overall and stratified by RTT type and age



[a]Proportions of individuals with incident g-tube surgery were evaluated among individuals without a baseline g-tube surgery (overall cohort: N = 350; classic RTT: N = 314; atypical RTT: N = 36; pediatric: N = 275; adult: N = 75); [b]G-tube surgeries included endoscopic gastrostomy, gastrostomy with fundoplication, and gastrostomy without fundoplication
G-tube, gastrostomy tube; RTT, Rett syndrome

Treatment Patterns During the Observation Period

- Overall, prokinetic agents were the most used pharmacological therapy (39.8%), followed by antiepileptic drugs (32.3%), sedatives/hypnotics (25.3%), and nutritional supplements (23.1%). These findings were consistent across subgroups (**Table 2**)
- The most common reason for stopping prokinetic agents and sedative/hypnotics was that the therapy was no longer needed (63.0% and 44.0%, respectively). Among individuals who stopped antiepileptic drugs, nearly half (48.8%) stopped use due to ineffective treatment (**Table 2**)

Table 2. Pharmacological treatment patterns among females with RTT, overall and stratified by RTT type and age

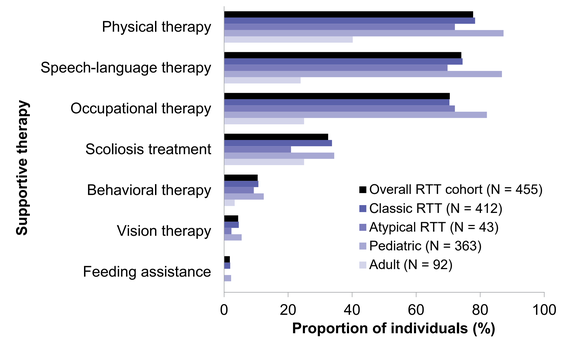
Pharmacological therapies,[a] n (%)	Overall RTT cohort (N = 455)	Stratification by RTT type[b]		Stratification by age[c]	
		Classic RTT (N = 412)	Atypical RTT (N = 43)	Pediatric (<18 years of age) (N = 363)	Adult (≥18 years of age) (N = 92)
Prokinetic agents	181 (39.8)	164 (39.8)	17 (39.5)	155 (42.7)	26 (28.3)
Individuals who stopped use[d]	46 (25.4)	44 (26.8)	2 (11.8)	43 (27.7)	3 (11.5)
Reasons for stopping[e]					
Ineffective	11 (23.9)	10 (22.7)	1 (50.0)	11 (25.6)	0
Not needed	29 (63.0)	28 (63.6)	1 (50.0)	28 (65.1)	1 (33.3)
Side effects	10 (21.7)	10 (22.7)	0	8 (18.6)	2 (66.7)
Missing[f]	2 (4.3)	2 (4.5)	0	2 (4.7)	0
Antiepileptic drugs	147 (32.3)	137 (33.3)	10 (23.3)	127 (35.0)	20 (21.7)
Individuals who stopped use[d]	41 (27.9)	40 (29.2)	1 (10.0)	36 (28.3)	5 (25.0)
Reasons for stopping[e]					
Ineffective	20 (48.8)	20 (50.0)	0	17 (47.2)	3 (60.0)
Not needed	10 (24.4)	10 (25.0)	0	9 (25.0)	1 (20.0)
Side effects	13 (31.7)	12 (30.0)	1 (100)	12 (33.3)	1 (20.0)
Missing[f]	3 (7.3)	3 (7.5)	0	3 (8.3)	0
Sedative/hypnotics	115 (25.3)	101 (24.5)	14 (32.6)	101 (27.8)	14 (15.2)
Individuals who stopped use[d]	25 (21.7)	23 (22.8)	2 (14.3)	23 (22.8)	2 (14.3)
Reasons for stopping[e]					
Ineffective	9 (36.0)	8 (34.8)	1 (50.0)	8 (34.8)	1 (50.0)
Not needed	11 (44.0)	10 (43.5)	1 (50.0)	11 (47.8)	0
Side effects	9 (36.0)	8 (34.8)	1 (50.0)	7 (30.4)	2 (100)
Missing[f]	1 (4.0)	1 (4.3)	0	1 (4.3)	0
Nutritional supplements	105 (23.1)	95 (23.1)	10 (23.3)	91 (25.1)	14 (15.2)
Individuals who stopped use[d]	20 (19.0)	19 (20.0)	1 (10.0)	20 (22.0)	0
Reasons for stopping[e]					
Ineffective	1 (5.0)	1 (5.3)	0	1 (5.0)	0
Not needed	16 (80.0)	15 (78.9)	1 (100)	16 (80.0)	0
Side effects	3 (15.0)	2 (10.5)	1 (100)	3 (15.0)	0
Missing[f]	1 (5.0)	1 (5.3)	0	4 (20.0)	0

[a]Pharmacological therapies were identified using the treatment condition listed in the medication log data. For example, any medication listed as being a treatment for "gastric motility" was classified as a prokinetic agent; [b]Classic or atypical diagnosis of RTT was identified at the time of study enrollment based on the latest consensus criteria for RTT; [c]Age was assessed at the date of first visit; [d]The percentage of individuals stopping use of a drug class of interest was calculated only among individuals with use of the drug class of interest; [e]Individuals could have multiple reasons for stopping a treatment, so categories of reasons for stopping a treatment are not mutually exclusive and will not sum to the total number of individuals who stopped the respective treatment; [f]Individuals were considered to have a missing reason for stopping treatment if they were observed to have stopped treatment but no reason for stopping treatment was listed

RTT, Rett syndrome

- Physical therapy was the most used supportive therapy overall (77.8%), followed by speech-language therapy (74.1%) and occupational therapy (70.5%). All supportive therapies were more common among pediatric individuals relative to adults, and the largest differences were observed for physical therapy (87.3% vs 40.2%, respectively), speech-language therapy (86.8% vs 23.9%, respectively), and occupational therapy (82.1% vs 25.0%, respectively). Use of supportive therapies was generally consistent between individuals with classic RTT and atypical RTT (**Figure 2**).

Figure 2. Supportive therapies[a,b] used among females with RTT, overall and stratified by RTT type and age



[a]Scoliosis treatment included bracing, serial casting, and surgery; [b]Individuals were identified as having feeding assistance supportive therapy if they had a hospital or emergency room visit with feeding assistance listed as the reason for the visit
RTT, Rett syndrome

STUDY LIMITATIONS

- Endpoints of interest, such as supportive therapy use, were reported by caregivers. Given the subjectivity of these endpoints, there is the potential for recall bias and misspecification
- There were missing data in the 5211 RNHS data; if data are not systematically captured across all individuals, this can lead to underestimation of endpoints
- Findings may not be generalizable to individuals with RTT from minority populations in the United States given the largely White population represented in this study

CONCLUSIONS

- Across RTT types and age groups, individuals with RTT have large unmet needs: most individuals require supportive therapy, and nearly half of all individuals require hospital/emergency room visits and pharmacological therapies
- Both RTT-related outcomes and treatment use were higher among pediatric than adult individuals, suggesting a need for symptom management earlier in the lifespan of individuals with RTT
- These findings underscore the substantial disease burden of RTT and highlight opportunities for novel treatments to provide clinical benefit across a variety of RTT symptoms

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DISCLOSURES

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