Real-world Clinical Management of Individuals With Rett Syndrome: A Physician Survey

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INTRODUCTION

- Rett syndrome (RTT) is a severe neurodevelopmental disorder predominantly affecting girls, characterized by multisystem comorbidities[1]
- There is considerable heterogeneity in the clinical trajectories, profiles, and manifestations among individuals with RTT
- Additionally, there are no approved therapies targeting the underlying cause of RTT; thus, all available treatment strategies are aimed at managing symptoms,[2,3] making the treatment approach highly heterogeneous and individually tailored, with a lack of a clear consensus on how to define success in treating RTT[1]
  - This can result in considerable burden, both on the health system and on individuals with RTT and their caregivers
- There is limited literature on the clinical profiles, clinical burden, healthcare use patterns, and management strategies in individuals with RTT in the United States
- To address this, the present study gauged the perspectives of physicians with experience managing RTT (i.e., RTT-treating physicians), with the aim of providing a contemporary description of the clinical profiles, clinical manifestations, healthcare use patterns, treatment goals, and management strategies among individuals with RTT in the United States

METHODS

Study Design

- This study employed a mixed-methods research approach that involved the sequential use of qualitative and quantitative methods; the first was used to help inform the design of the second
- During the qualitative phase, in-depth individual interviews were conducted with 5 RTT-treating physicians to gain a broad understanding of RTT clinical management and to extract key themes
- In the quantitative phase, the data from the interviews guided the development of a cross-sectional survey through which RTT-treating physicians reported on the clinical profiles, manifestations, and treatment strategies among individuals with RTT under their care
  - The planned recruitment for the quantitative survey was 100 RTT-treating physicians, evenly split between pediatricians and neurologists

Study Population

- To be eligible for this study, physicians were required to meet all of the following criteria: (1) practicing neurologist or pediatrician in the United States, (2) experienced in treating ≥2 individuals with RTT at any time, (3) treated ≥1 individual with RTT in the past 2 years, and (4) willing to provide informed consent to participate in the study
- Given that RTT is predominantly diagnosed among females, physicians who had seen an unexpected number (i.e., ≥2) or distribution (i.e., ≥20%) of male individuals with RTT in their care were excluded

Statistical Analysis

- During the qualitative phase, transcripts from the in-depth interviews were reviewed to identify and describe major themes; these were used to guide the development of the quantitative survey
- The quantitative survey collected information on physician characteristics and experience, demographics and clinical profiles of individuals with RTT, clinical manifestations and symptoms, healthcare use patterns, and treatment goals and management strategies
- Results were summarized using descriptive statistics overall and stratified by the specialties of the RTT-treating physicians, specifically: pediatricians (including developmental pediatricians) and neurologists (including pediatric neurologists, neurologists who were also geneticists, and neurologists who were also RTT specialists)

RESULTS

Study Population

- After applying all eligibility criteria, 100 RTT-treating physicians completed the survey in the quantitative phase, including 51 neurologists and 49 pediatricians

Physician Characteristics and Experience Managing RTT (Table 1)

- Surveyed physicians had spent a mean of 19.3 years in their specialty after their residency
- A large proportion of neurologists were based in academic/university medical centers (43.1%), while most pediatricians worked in private practice (67.3%)
- Neurologists had treated more individuals with RTT than pediatricians throughout their career (23.5 versus 6.8 individuals, respectively) and in the past 2 years (10.8 versus 2.5 individuals, respectively)
- Most physicians were comfortable managing RTT, with more neurologists than pediatricians indicating being comfortable (78.5% versus 44.9%, respectively, indicated they were somewhat or very comfortable)
- Experience in diagnosing RTT was indicated by 93.0% of physicians; almost all these physicians evaluated symptoms (91.4%) or used genetic testing (86.0%) for RTT diagnoses
  - Neurologists were more likely to use the 2010 consensus diagnostic criteria than pediatricians (54.2% versus 28.9%, respectively)
- Most physicians (87.1%) typically considered an alternative diagnosis, with the most common differential diagnoses being autism spectrum disorder (86.4%), nonspecific developmental delay (60.5%), and Angelman syndrome (54.3%)

Table 1. Physician characteristics and experience managing RTT[a,b]

	All physicians (N = 100)	Neurologists (n = 51)	Pediatricians (n = 49)
Years in specialty (after residency)	19.3 ± 9.0 (19.0)	17.1 ± 8.4 (16.0)	21.6 ± 9.2 (23.0)
Type of institution, n (%)			
Private practice	48 (48.0)	15 (29.4)	33 (67.3)
Academic/university medical center	29 (29.0)	22 (43.1)	7 (14.3)
Community-based hospital	12 (12.0)	9 (17.6)	3 (6.1)
Community clinic	9 (9.0)	5 (9.8)	4 (8.2)
Number of individuals with RTT treated throughout career (8.0)	**15.3 ± 23.7 (8.0)**	**23.5 ± 30.3 (12.0)**	**6.8 ± 7.4 (5.0)**
Number treated in the past 2 years	6.7 ± 11.7 (3.0)	10.8 ± 15.3 (5.0)	2.5 ± 2.4 (2.0)
Comfort level managing individuals with RTT, n (%)			
1—Not comfortable	1 (1.0)	0 (0.0)	1 (2.0)
2—Somewhat not comfortable	8 (8.0)	3 (5.9)	5 (10.2)
3—Neither comfortable nor not comfortable	29 (29.0)	8 (15.7)	21 (42.9)
4—Somewhat comfortable	44 (44.0)	24 (47.1)	20 (40.8)
5—Very comfortable	18 (18.0)	16 (31.4)	2 (4.1)
Number of physicians with experience diagnosing RTT	**N = 93**	**n = 48**	**n = 45**
Criteria/tests used to assign/confirm diagnosis, n (%)			
Evaluation of patients' symptoms	85 (91.4)	43 (89.6)	42 (93.3)
Genetic testing	80 (86.0)	43 (89.6)	37 (82.2)
The 2010 consensus diagnostic criteria[c]	39 (41.9)	26 (54.2)	13 (28.9)
The 2002 consensus diagnostic criteria[d]	10 (10.8)	4 (8.3)	6 (13.3)
Other diagnostic tools (e.g., imaging, lab values)	28 (30.1)	16 (33.3)	12 (26.7)
Typically assign RTT classification (classic/variant), n (%)			
No	50 (53.8)	23 (47.9)	27 (60.0)
Yes	32 (34.4)	23 (47.9)	9 (20.0)
Unknown/not sure	11 (11.8)	2 (4.2)	9 (20.0)
Typically consider alternative diagnoses, n (%)	81 (87.1)	42 (87.5)	39 (86.7)
Top 5 alternative diagnoses considered, n (%)			
Autism spectrum disorder	70 (86.4)	34 (81.0)	36 (92.3)
Nonspecific developmental delay	49 (60.5)	22 (52.4)	27 (69.2)
Angelman syndrome	44 (54.3)	25 (59.5)	19 (48.7)
Cerebral palsy	36 (44.4)	18 (42.9)	18 (46.2)
CDKL5 mutation	28 (34.6)	23 (54.8)	5 (12.8)

[a]Mean ± SD (median) values shown unless otherwise stated; [b]"Other" response options as well as response options selected by ≤5 respondents have not been shown; [c]Neul JL, et al.[1]; [d]Hagberg B, et al.[5]
CDKL5, cyclin-dependent kinase-like 5; RTT, Rett syndrome; SD, standard deviation

Demographic and Clinical Profiles of Individuals With RTT (Table 2)

- As expected, surveyed physicians reported that the vast majority (96.0%) of individuals with RTT in their care were female
- Most individuals treated by the surveyed physicians were diagnosed at earlier RTT disease stages (stage I: 42.1%; stage II: 31.9%) and were young at diagnosis (<2 years: 19.9%; 2–<5 years: 41.7%)
  - However, substantial proportions of individuals were diagnosed later in the disease trajectory (25.6% of individuals diagnosed at stages III–IV) and were comparatively older (38.2% were ≥5 years of age)

Healthcare Use Patterns and Disease Management Among Individuals With RTT (Table 3)

- Most physicians saw the individuals with RTT under their care at least every 6 months, especially younger individuals (>94.1% for individuals <5 years of age versus 68.7% for those ≥20 years of age)
- The most common factors that increased the frequency with which physicians saw individuals with RTT were severity of symptoms (88.0%), younger age of the individual (65.0%), and individual's/caregiver's preference (57.0%)
- The majority of neurologists were referred individuals with RTT by general pediatricians (68.6%) and primary care physicians (68.6%); in contrast, many pediatricians were already seeing individuals with RTT when symptoms appeared (34.7%)
- Most individuals with RTT under the care of surveyed physicians saw other healthcare professionals for disease management, most commonly behavioral therapists/psychologists/psychiatrists (75.0%), speech therapists (66.0%), or physical therapists (65.0%)
- The majority of physicians (60.0%) used clinical practice guidelines to monitor the progress of individuals with RTT; when recommending treatments for symptom control, the top considerations were age of the individual (80.0%), disease stage (76.0%), and preference of the individual with RTT/family/caregiver (71.0%)

Table 2. Real-world demographic and clinical profiles of individuals with RTT

	All physicians (N = 100)
Percentage of females with RTT managed by the physicians	96.0 ± 12.7
Percentage of individuals with RTT managed by the physicians at each disease stage at the time of RTT diagnosis[a,b]	
Stage I	42.1 ± 35.3 (38.0)
Stage II	31.9 ± 29.2 (29.0)
Stage III	17.7 ± 23.5 (3.3)
Stage IV	7.9 ± 14.9 (0.0)
Unknown disease stage	14.6 ± 34.5 (0.0)
Percentage of individuals with RTT managed by the physicians in each age group at the time of RTT diagnosis[a,b]	
<2 years	19.9 ± 27.6 (0.0)
2 to <5 years	41.7 ± 29.8 (40.0)
5 to <12 years	23.9 ± 26.0 (20.0)
12 to <20 years	8.6 ± 16.9 (0.0)
≥20 years	5.7 ± 15.9 (0.0)
Unknown age	3.1 ± 17.2 (0.0)

[a]Mean ± SD (median) values shown unless otherwise stated; [b]Physicians did not provide responses for all disease stages and age groups, hence sample sizes ranged from 85 to 100 physicians across the individual stages and age groups
RTT, Rett syndrome; SD, standard deviation

Table 3. Healthcare use patterns and disease management among individuals with RTT[a,b]

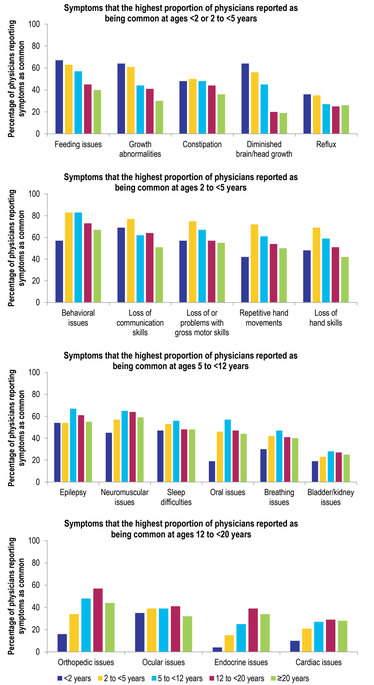
	All physicians (N = 100)	Neurologists (n = 51)	Pediatricians (n = 49)
Top 5 factors that increase the frequency at which physicians see individuals with RTT, n (%)			
Severity of symptoms	88 (88.0)	46 (90.2)	42 (85.7)
Younger age (i.e., younger individuals seen more frequently)	65 (65.0)	31 (60.8)	34 (69.4)
Preference of individual with RTT/family/caregiver for more frequent visits	57 (57.0)	25 (49.0)	32 (65.3)
Earlier disease stage (i.e., earlier stages seen more frequently)	33 (33.0)	18 (35.3)	15 (30.6)
Later disease stage (i.e., later stages seen more frequently)	15 (15.0)	7 (13.7)	8 (16.3)
Most common specialties of physicians who referred individuals with RTT to the respondents, n (%)			
General pediatrician	49 (49.0)	35 (68.6)	14 (28.6)
Primary care physician	48 (48.0)	35 (68.6)	13 (26.5)
Developmental pediatrician	30 (30.0)	20 (39.2)	10 (20.4)
Pediatric neurologist	25 (25.0)	13 (25.5)	12 (24.5)
Geneticist	20 (20.0)	10 (19.6)	10 (20.4)
General neurologist	14 (14.0)	11 (21.6)	3 (6.1)
None[c]	18 (18.0)	1 (2.0)	17 (34.7)
Percentage of individuals with RTT under the physician's care seeing other HCPs for disease management,[d] mean ± SD (median)	**91.5 ± 19.2 (100.0)**	**85.0 ± 24.1 (100.0)**	**96.9 ± 11.9 (100.0)**
Top 5 other specialists seen by individuals with RTT for disease management, n (%)			
Behavioral therapist/psychologist/psychiatrist	75 (75.0)	37 (72.5)	38 (77.6)
Speech therapist	66 (66.0)	32 (62.7)	34 (69.4)
Physical therapist	65 (65.0)	33 (64.7)	32 (65.3)
Pediatric neurologist	62 (62.0)	19 (37.3)	43 (87.8)
Occupational therapist	60 (60.0)	32 (62.7)	28 (57.1)
Clinical scales, tests, or guidelines typically used to monitor progress, n (%)			
Clinical practice guidelines	60 (60.0)	30 (58.8)	30 (61.2)
RTT-Clinical Severity Scale	34 (34.0)	21 (41.2)	13 (26.5)
Rett Syndrome Behaviour Questionnaire	25 (25.0)	14 (27.5)	11 (22.4)
Motor Behavior Assessment scale	18 (18.0)	12 (23.5)	6 (12.2)
None	17 (17.0)	7 (13.7)	10 (20.4)
Unknown/not sure	7 (7.0)	1 (2.0)	6 (12.2)
Top 5 factors considered when recommending treatment for symptom control, n (%)			
Age of the individual with RTT	80 (80.0)	38 (74.5)	42 (85.7)
Disease stage	76 (76.0)	38 (74.5)	38 (77.6)
Preference of individual with RTT/family/caregiver	71 (71.0)	33 (64.7)	38 (77.6)
Insurance coverage	58 (58.0)	30 (58.8)	28 (57.1)
Price/cost of treatment for the individual with RTT/family/caregiver	45 (45.0)	25 (49.0)	20 (40.8)

[a]Mean ± SD (median) values shown unless otherwise stated; [b]"Other" response options as well as response options selected by ≤5 respondents have not been shown; [c]Physician was already seeing the individual with RTT when RTT-like symptoms appeared; [d]Physicians who selected "unknown/unsure" for this question were excluded (n = 82, 37 neurologists, 45 pediatricians)
HCP, healthcare professional; RTT, Rett syndrome; SD, standard deviation

Physician Reports of Common Clinical Manifestations or Symptoms Among Individuals With RTT (Figure 1)

- Physicians were asked about common clinical manifestations, defined as symptoms the physicians reported seeing in >25% of individuals with RTT in their care in a given age group
  - Symptoms commonly seen by most physicians (i.e., reported by >50% of physicians in ≥1 age group) included feeding issues, growth abnormalities, repetitive hand movements, loss of hand skills, behavioral issues, loss of communication skills, loss of or problems with gross motor skills, epilepsy/seizures, and neuromuscular issues

Figure 1. Physician reports of common clinical manifestations or symptoms among individuals with RTT[a,b]



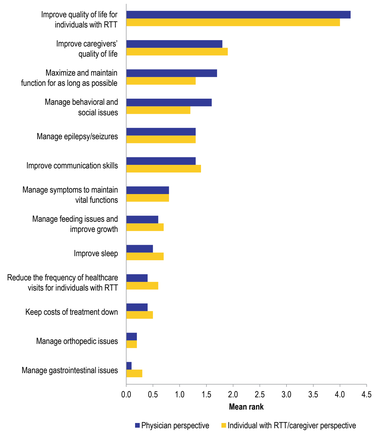
[a]Common symptoms were defined as those that physicians reported seeing among >25% of individuals with RTT in their care in a given age group; [b]Examples of symptoms in each category are as follows: feeding issues: chewing or swallowing dysfunction, growth abnormalities, poor weight gain; behavioral issues: anxiety or focus issues, irritability; loss of communication skills: loss of speech, abnormal speech, loss of language; loss of or problems with gross motor skills: sitting, crawling, walking, gait issues; repetitive hand movements: clapping, hand wringing, hand tapping; neuromuscular issues: body stiffening, dystonia; oral issues: bruxism, dental caries; breathing issues: breathing dysrhythmias, hyperventilation, breath-holding; bladder/kidney issues: urinary retention; orthopedic issues: contractures, scoliosis; ocular issues: abnormal eye movements, loss of eye contact; endocrine issues: altered menarche; cardiac issues: prolonged QT interval
RTT, Rett syndrome

- Smaller proportions of physicians indicated other symptoms as common (i.e., reported by <50% of physicians in all age groups), including breathing issues, bladder/kidney issues, ocular issues, endocrine issues, and cardiac issues
- Symptoms of RTT also showed distinct age-related trends, as evidenced by the proportions of physicians who commonly encountered these symptoms across different age groups
  - A higher proportion of physicians indicated that the following symptoms were common at <2 years of age versus the proportion of physicians reporting them as common at ≥20 years of age, respectively: feeding issues (67.6% versus 40.4%), growth abnormalities (64.7% versus 30.8%), constipation (48.5% versus 36.5%), diminished brain/head growth (64.7% versus 19.2%), and reflux (36.8% versus 26.9%)

RTT Treatment Goals From the Perspectives of Physicians and Individuals With RTT/Caregivers (Figure 2)

- From both the physicians' and the individuals with RTT/caregivers' perspectives, improving the quality of life of individuals with RTT was the most important goal, followed by improving caregivers' quality of life
- Other important treatment goals included maximizing and maintaining function for as long as possible, managing behavioral/social issues, managing epilepsy/seizures, and improving communication skills

Figure 2. Mean rank for RTT treatment goals from the perspectives of physicians and individuals with RTT/caregivers[a]



[a]Physicians provided a rank to these treatment goals by importance: each physician ranked up to 5 goals from 1 to 5, with 5 being the most important goal and 1 being the fifth most important goal; treatment goals not ranked were given a score of 0
RTT, Rett syndrome

Common Real-world Management Strategies (Table 4)

- The physicians most commonly treated behavioral issues, epilepsy/seizures, and feeding issues
- Treatment strategies varied by symptom: while pharmacological strategies (e.g., antiepileptic drugs) were commonly used to treat behavioral issues and epilepsy, feeding issues were mainly treated using nonpharmacological approaches (e.g., occupational and speech therapy)
- For all symptoms, referral to appropriate specialists was common
- A large proportion of physicians (36.8%) identified the lack of disease-modifying therapies and reliance on symptom-specific management as an unmet need

Table 4. Common real-world management strategies for the top 3 symptoms managed by the surveyed physicians[a]

Strategies, n (%)	All physicians	Neurologists	Pediatricians
Behavioral issues (e.g., anxiety, hysteria, irritability)	**N = 67**	**n = 35**	**n = 32**
Antiseizure/antiepileptic medications	42 (62.7)	23 (65.7)	19 (59.4)
Antianxiety medications	41 (61.2)	24 (68.6)	17 (53.1)
Referral to behavioral therapist/psychologist/psychiatrist	41 (61.2)	19 (54.3)	22 (68.8)
Medications that work on the serotonin system	28 (41.8)	18 (51.4)	10 (31.3)
Management by social worker	13 (19.4)	8 (22.9)	5 (15.6)
Epilepsy/seizures	**N = 63**	**n = 44**	**n = 19**
Antiseizure/antiepileptic medications	56 (88.9)	41 (93.2)	15 (78.9)
Antianxiety medications	31 (49.2)	25 (56.8)	6 (31.6)
Ketogenic diet	25 (39.7)	22 (50.0)	3 (15.8)
Referral to epileptologist/neurologist	22 (34.9)	9 (20.5)	13 (68.4)
Vagus nerve stimulation	20 (31.7)	19 (43.2)	1 (5.3)
General neurologist	14 (22.2)	11 (25.0)	3 (15.8)
Feeding issues (e.g., chewing/swallowing dysfunction)	**N = 33**	**n = 6**	**n = 27**
Occupational therapy	20 (60.6)	2 (33.3)	18 (66.7)
Speech therapy	20 (60.6)	2 (33.3)	18 (66.7)
Supplements (e.g., levocarnitine, PediaSure)	19 (57.6)	2 (33.3)	17 (63.0)
Referral to nutritionist	17 (51.5)	4 (66.7)	13 (48.1)
Gastrostomy tube	13 (39.4)	3 (50.0)	10 (37.0)

[a]"Other" response options as well as response options selected by ≤5 respondents have not been shown

LIMITATIONS

- The quantitative phase of this study was subject to common limitations of surveys, including differences between participants in the interpretation of the survey questions
- The study relied on physicians' experiences treating individuals with RTT when reporting data, which could be subject to recall error
- Although this study surveyed 100 physicians from a range of backgrounds (including both pediatricians and neurologists), the results of the survey may not be generalizable to physicians outside of the sample studied

CONCLUSIONS

- RTT is associated with a substantial burden of disease, as evidenced by frequent healthcare use and multiple clinical manifestations that vary according to age and are typically managed using symptom-specific strategies
- The results underscore a major unmet need in RTT: the lack of novel treatments that are disease-modifying or treatments that can improve the quality of life of individuals with RTT and their caregivers

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