Patient Journey and Clinical Burden of Rett Syndrome in the United States

Damian May,[1] Kalé Kponee-Shovein,[2] Malena Mahendran,[2] Nathaniel Downes,[2] Kristy Sheng,[2] Patrick Lefebvre,[2] Wendy Y. Cheng[2]

[1]Acadia Pharmaceuticals Inc., San Diego, CA, USA; [2]Analysis Group, Inc., Boston, MA, USA

INTRODUCTION

- Rett syndrome (RTT) is a severe neurodevelopmental disorder that almost exclusively affects girls[1]
- Patients with RTT often require lifelong care due to a variety of symptoms, ranging from mild to severe, including neurological, gastrointestinal, cardiac, endocrine, and orthopedic disorders[2]
- To date, there is no cure for RTT, and current treatment options are aimed at managing symptoms and supporting daily activities[3]
- There is limited literature on the clinical burden associated with RTT in the United States, representing a much-needed area of study
- To add to the literature on RTT, this study aimed to provide an overview of the patient journey and clinical burden of RTT with respect to baseline characteristics, clinical manifestations, and treatment patterns among female individuals in the US

METHODS

Data Source

- Administrative healthcare claims data from the IQVIA™ Medical Claims Data (Dx) and Longitudinal Prescription Data (LRx) databases were used to address the study objectives

Study Design

- A longitudinal, retrospective, cohort study was used to address the study objectives (November 1, 2016–October 31, 2019)
- The index date was defined as the date of the first observed diagnosis of RTT
- The baseline period was defined as 6 months prior to the index date for patients ≥1 year old or from the start of clinical activity to the index date for patients <1 year old and was used to describe demographic and clinical characteristics
- The observation period was defined as the period from the index date to the earliest of either the end of clinical activity or the end of data availability, during which clinical manifestations and treatment patterns were described

Study Population

- Females with ≥1 medical claim with a primary or secondary diagnosis code of RTT were included. Those with medical claims for cerebrovascular disease or brain trauma during the baseline period were excluded
- Individuals were further stratified into pediatric (<18 years of age on index) and adult (≥18 years of age on index) subgroups

Statistical Analysis

- Description of baseline demographic and clinical characteristics:
  - Continuous characteristics were summarized using means, standard deviations, and medians
  - Categorical characteristics were summarized using relative frequencies and proportions
- Frequency of common clinical manifestations and treatment patterns following RTT diagnosis:
  - The prevalences of clinical manifestations and therapies were described using relative frequencies and proportions
  - Clinical manifestations were described by age as the number of clinical manifestation events and the proportion of patients with ≥1 clinical manifestation per year using a panel plot
  - Treatment patterns during the observation period were described by age as the proportion of patients with ≥1 use of a treatment per year using a panel plot
  - Extreme values were truncated at the 5th and 95th percentiles to reduce sensitivity to outliers

RESULTS

Study Population

- After applying all eligibility criteria, 5,940 females were included in the study population, of whom 3,078 (52%) comprised the pediatric cohort and 2,862 (48%) comprised the adult cohort

Baseline Demographic and Clinical Characteristics

- Median age of the overall RTT cohort was 17.0 years (interquartile range: 9–28 years) and most individuals were from the South (34.5%). Among specified insurance plan types, Medicaid was most common (27.3%). Frequency of *MECP2* genetic testing prior to the index RTT diagnosis was low (1.2%; **Table 1**)
- Overall, 16.2% of patients (pediatric: 19.9%; adult: 12.2%) had ≥1 differential diagnosis prior to their index RTT diagnosis, primarily as nonspecific developmental delay (9.2%) or autism spectrum disorder (8.7%) among the pediatric cohort, and as cerebral palsy (8.5%) among the adult cohort

Frequency of Common Clinical Manifestations Following RTT Diagnosis

- Over a mean observation period of 2.04 years, the most prevalent clinical manifestations among female individuals with RTT were neurological disorders (72.8%), primarily driven by epilepsy (52.1%; data not shown), followed by gastrointestinal and nutritional disorders (41.9%) and orthopedic disorders (34.6%; **Table 2**)
- Based on the panel plot data, the prevalence and number of neurological and gastrointestinal manifestation events were generally highest in early childhood (1–3 years of age) before decreasing and reaching a plateau into early adulthood (~26 years of age; **Figure 1**). Conversely, orthopedic events were highest in adolescence (~13 years of age)

Treatment Patterns Following RTT Diagnosis

- Feeding assistance was the most prevalent supportive therapy overall (37.9%) and for pediatric (43.3%) and adult individuals (32.2%), followed by physical therapy (33.3%) for the pediatric cohort and other home/hospice care (25.1%) for the adult cohort. The prevalence of speech-language therapy (13.3%) was primarily driven by the pediatric cohort (pediatric: 21.7%; adult: 4.3%; **Table 3**)
- Antiepileptic drugs were the most prevalent pharmacological therapy used (54.8%; **Table 3**), with use peaking at 26 years of age and sustained into later adulthood (data not shown). Use of other pharmacologic agents was generally low
- Based on panel plot data, use of physical, speech-language, and occupational therapies was highest during early childhood (3–4 years of age) before decreasing in use by over 50% by age 18. Use of feeding assistance grew over childhood and was most prevalent during adolescence (12–17 years of age), while use of home/hospice care remained relatively stable across all ages (**Figure 2**)

Table 1. Baseline demographics and clinical characteristics among patients with RTT, overall and by pediatric and adult patients

Characteristics	Overall RTT cohort N = 5,940	Stratification by age: Pediatric (<18 years of age) n = 3,078	Stratification by age: Adult (≥18 years of age) n = 2,862
Demographics[a]			
Age at index date, years, median (IQR)	17.0 (9–28)	9.0 (5–13)	29.0 (22–37)
Region, n (%)			
South	2,051 (34.5)	1,155 (37.5)	896 (31.3)
West	1,373 (23.1)	716 (23.3)	657 (23.0)
Midwest	1,328 (22.4)	648 (21.1)	680 (23.8)
Northeast	1,151 (19.4)	538 (17.5)	613 (21.4)
Other[b]	4 (0.1)	2 (0.1)	2 (0.1)
Unknown/unspecified	33 (0.6)	19 (0.6)	14 (0.5)
Insurance plan type, n (%)			
Unknown/unspecified plan[c]	1,658 (27.9)	998 (32.4)	660 (23.1)
Medicaid	1,621 (27.3)	858 (27.9)	763 (26.7)
Commercial	1,101 (18.5)	675 (21.9)	426 (14.9)
Medicare/Medicaid Dual Eligible	895 (15.1)	528 (17.2)	367 (12.8)
Medicare	665 (11.2)	19 (0.6)	646 (22.6)
Quan-CCI,[d,e] mean ± SD [median]	0.1 ± 0.4 [0.0]	0.1 ± 0.3 [0.0]	0.1 ± 0.5 [0.0]
***MECP2* genetic testing,[d,f] n (%)**	69 (1.2)	61 (2.0)	8 (0.3)
Rendering provider specialty,[g,h] n (%)			
Unknown/missing	41 (59.4)	37 (60.7)	4 (50.0)
Pediatrician/pediatric specialist[i]	16 (23.2)	14 (23.0)	2 (25.0)
Genetics/pathology specialist	7 (10.1)	7 (11.5)	0 (0.0)
Primary care	4 (5.8)	2 (3.3)	2 (25.0)
Neurologist	1 (1.4)	1 (1.6)	0 (0.0)
Differential diagnosis of RTT,[d] n (%)			
Any differential diagnosis	963 (16.2)	613 (19.9)	350 (12.2)
Autism spectrum disorder	367 (6.2)	269 (8.7)	98 (3.4)
Cerebral palsy	413 (7.0)	171 (5.6)	242 (8.5)
Nonspecific developmental delay	321 (5.4)	284 (9.2)	37 (1.3)
Angelman syndrome	2 (0.0)	2 (0.1)	0 (0.0)
Other childhood disintegrative disorder	6 (0.1)	3 (0.1)	3 (0.1)

[a]Evaluated on the index date (ie, date of the first observed medical claim with a diagnosis of RTT); [b]Includes Puerto Rico, Virgin Islands, and Guam; [c]Includes medical claims associated with an unspecified plan, unknown third party, cash, claims processing, or missing; [d]Evaluated on each distinct day during the baseline period and including the index date; [e]Quan H, et al.[4]; Identified using CPT codes: 81332–81334, 02340, 81470, 81471, 81479; [f]*MECP2* genetic testing date was based on the medical claim associated with a procedure code for *MECP2* genetic testing closest to the index date and including on the index date; [g]Based on the specialty of the provider who rendered the service of medical claims associated with a procedure code for *MECP2* genetic testing; [h]Pediatric specialist included child neurology, developmental/behavioral pediatrics, pediatric cardiology, pediatric endocrinology, pediatric gastroenterology, and pediatric radiology

CPT, Current Procedural Terminology; IQR, interquartile range; Quan-CCI, Quan-Charlson comorbidity index; RTT, Rett syndrome; SD, standard deviation

Table 2. Frequency of clinical manifestations among patients with RTT, overall and by pediatric and adult patients

Clinical manifestations[a]	Patients with ≥1 clinical manifestation (%): Overall RTT cohort N = 5,940	Stratification by age: Pediatric (<18 years of age) n = 3,078	Stratification by age: Adult (≥18 years of age) n = 2,862
Observation period,[b] years, mean ± SD [median]	2.04 ± 0.96 [2.4]	2.04 ± 0.98 [2.4]	2.04 ± 0.95 [2.4]
Neurological disorders	4,323 (72.8)	2,366 (76.9)	1,957 (68.4)
Gastrointestinal and nutritional disorders	2,489 (41.9)	1,373 (44.6)	1,116 (39.0)
Orthopedic disorders	2,054 (34.6)	1,118 (36.3)	936 (32.7)
Oral disorders[c]	582 (9.8)	287 (9.3)	295 (10.3)
Endocrine disorders	312 (5.3)	88 (2.9)	224 (7.8)
Prolonged QT interval	132 (2.2)	94 (3.1)	38 (1.3)

[a]Clinical manifestation events were defined as any day during which an *ICD-10-CM* code for a clinical manifestation was observed; [b]The follow-up period was defined as the period from the index date (ie, date of the first observed medical claim with a diagnosis of RTT) to the earliest of either the end of clinical activity or the end of data availability (ie, October 31, 2019); [c]Frequency of oral disorders were evaluated using medical benefit claims only and may be underestimated if patients had third-party dental insurance

ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; RTT, Rett syndrome; SD, standard deviation

Figure 1. Average number and percentage of patients with yearly clinical manifestations by age during the follow-up period, all patients

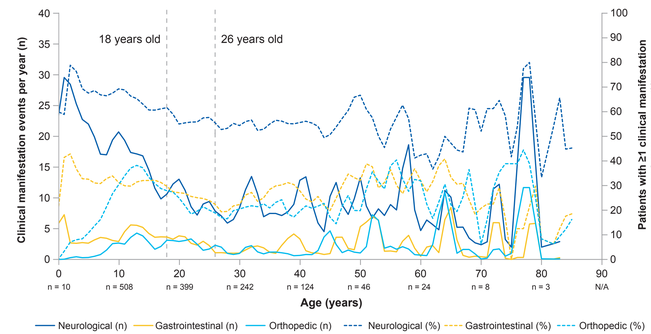


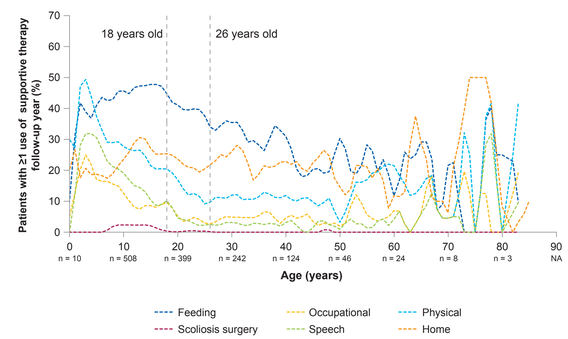
Table 3. Treatment patterns among patients with RTT, overall and by pediatric and adult patients

Treatment patterns	Overall RTT cohort N = 5,940	Stratification by age: Pediatric (<18 years of age) n = 3,078	Stratification by age: Adult (≥18 years of age) n = 2,862
Observation period,[a] years, mean ± SD [median]	2.04 ± 0.96 [2.42]	2.04 ± 0.98 [2.42]	2.04 ± 0.95 [2.42]
Supportive therapy			
Feeding assistance	2,253 (37.9)	1,332 (43.3)	921 (32.2)
Other home/hospice care	1,482 (24.9)	765 (24.9)	717 (25.1)
Physical therapy	1,450 (24.4)	1,024 (33.3)	426 (14.9)
Speech-language therapy	791 (13.3)	668 (21.7)	123 (4.3)
Occupational therapy	681 (11.5)	508 (16.5)	173 (6.0)
Scoliosis surgery	70 (1.2)	65 (2.1)	5 (0.2)
Hydrotherapy	0 (0.0)	0 (0.0)	0 (0.0)
Pharmacologic agents			
Antiepileptic drugs	3,258 (54.8)	1,703 (55.3)	1,555 (54.3)
Sedatives/hypnotics	407 (6.9)	156 (5.1)	251 (8.8)
Prokinetic agents	74 (1.2)	17 (0.6)	57 (2.0)
Nutritional supplements	32 (0.5)	12 (0.4)	20 (0.7)
Antiarrhythmic drugs	4 (0.1)	3 (0.1)	1 (0.0)

[a]The follow-up period was defined as the period from the index date (ie, date of the first observed medical claim with a diagnosis of RTT) to the earliest of either the end of clinical activity or the end of data availability (ie, October 31, 2019).

RTT; Rett syndrome; SD, standard deviation

Figure 2. Percentage of patients with yearly supportive therapies by age during the observation period, all patients



STUDY LIMITATIONS

- Patient enrollment data are not available in the IQVIA Dx and LRx databases. As such, continuous enrollment could not be established, and endpoints of interest may be underestimated
- Reliance on codes associated with medical claims may result in misclassification of patients and endpoints of interest
- Study findings may not be generalizable to individuals who have no insurance

CONCLUSIONS

- Patients with RTT have substantial concomitant disease burden across their lifespan, as evidenced by the high prevalence of clinical manifestations as well as reliance on both pharmacological and supportive therapy
- These findings underscore the unmet need for effective therapies to treat RTT, with the potential to reduce overall disease burden

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ACKNOWLEDGMENTS

This study was supported by Acadia Pharmaceuticals Inc. Medical writing support was provided by Stuart Murray, MSc, of Evidence Scientific Solutions (Horsham, UK) and Sewell Creative and funded by Acadia Pharmaceuticals Inc.

DISCLOSURES

KKS, **MM**, **ND**, **KS**, **PL**, and **WYC** are employees of Analysis Group., Inc., a consultancy that received funding from Acadia Pharmaceuticals Inc. to conduct this study.

DM is an employee of Acadia Pharmaceuticals Inc.

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Damian May (dmay@acadia-pharm.com)