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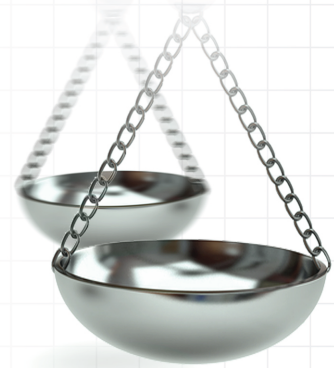

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Gastrointestinal manifestations in pediatric and adult patients with Rett syndrome: an analysis of US claims and physician survey data

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Aim: Patients with Rett syndrome (RTT) experience gastrointestinal (GI) manifestations. This study aimed to describe the prevalence of GI manifestations and the associated medical costs in patients with RTT in the USA. **Patients & Methods:** The study combined an insurance claims database analysis with a survey of 100 physicians experienced in RTT management. **Results:** GI manifestations affected 43.0% of 5940 patients, with increased prevalence in pediatric patients (45.6%) relative to adult patients (40.2%). Annualized mean medical cost of managing GI manifestations was $4473. Only 5.9–8.2% of neurologists and pediatricians ranked GI symptom management among the five most important treatment goals. **Conclusion:** Patients with RTT experience a high burden of GI manifestations, which translate to considerable medical costs. Importantly, the prevalence of GI manifestations was likely underestimated in this study, as only those symptoms which resulted in a healthcare encounter were captured.

Plain language summary

What is this article about? Rett syndrome (RTT) is a rare and severe neurodevelopmental disorder that almost exclusively affects girls and women. Patients with RTT develop debilitating symptoms that evolve throughout their lifespan, rendering them severely disabled. Gastrointestinal (GI) manifestations are common in patients with RTT and add to patient burden and caregiver concerns. This study described the prevalence of GI manifestations of RTT and the associated physician perspectives and medical costs in pediatric (<18 years) and adult patients.

What were the results? In an analysis of insurance claims data from the USA, GI manifestations were found to affect 43.0% of all patients and were slightly more common in pediatric patients (45.6%) relative to adult patients (40.2%). Mean medical costs of managing GI manifestations amounted to $4473 per patient per year (PPPY) and were somewhat higher in pediatric ($5530 PPPY) than adult ($3341 PPPY) patients. In a survey of 100 US physicians experienced in RTT management, only 5.9% of neurologists and 8.2% of pediatricians ranked management of GI manifestations among the five most important RTT treatment goals.

What do the results of the study mean? This study suggests that both pediatric and adult patients with RTT experience a high burden of GI manifestations, which are also associated with considerable medical costs. It is possible to proactively address GI manifestations as part of current routine care, although management of GI symptoms remains under-represented as an RTT treatment goal among treating physicians.

Tweetable abstract: Rett syndrome (RTT) is a rare and debilitating genetic disease. By combining claims data with a physician survey, we report on the prevalence, costs, and physicians' management strategies of gastrointestinal symptoms associated with RTT.

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Rett syndrome (RTT) is a severe neurodevelopmental disorder that almost exclusively affects girls and women [1]. It is a rare disease, with an estimated incidence of 1 out of every 10,000 to 15,000 live female births worldwide [1]. The most common form of RTT, occurring in 90–95% of patients, is caused by loss-of-function mutations in the X-linked *MECP2* gene [2].

RTT is characterized by normal early development followed by regression beginning around 12–18 months of age with a loss of speech and motor skills [2]. Patients develop debilitating symptoms, such as stereotypic hand movements, ataxia, autonomic and respiratory dysfunction, seizures and anxiety [2]. These multisystem comorbidities evolve throughout the patient's lifespan, rendering them severely disabled with reduced mobility, scoliosis and muscle weakness, rigidity, spasticity and abnormal posturing [1]. Almost 40% of adult women with RTT are unable to walk, even with assistance [3], and loss of ambulation has been shown to be a risk factor for increased mortality [4].

Historically, the prognosis of patients with RTT was bleak. Among the original cohort of patients born in the 1950s and 1960s described by Andreas Rett, only 31% survived until the age of 20 years and the median age at death was 13 years and 4.8 months [5]. However, recent real-world studies examining the natural history of RTT have reported substantially improved survival, with 77.6%–95% of patients surviving until age 20 [3,4], and up to 70% surviving until age 50 [4]. In the absence of curative therapy [1], and considering that several modifiable factors such as low weight, frequent seizures, and poor ambulation have been identified as risk factors for mortality [4], these improvements in survival have likely been driven by improved management of symptoms. Indeed, the historical reports on mortality in RTT preceded the implementation of intense therapeutic approaches [4]. Despite the improvements in management of RTT to date, there remains an ongoing need to better understand and optimally manage manifestations of RTT to ensure both improved survival and quality of life.

Gastrointestinal (GI) manifestations are common in patients with RTT, and may arise secondary to reduced GI motility (e.g., gastro-esophageal reflux disease [GERD] and constipation), as well as autonomic dysfunction (e.g., abdominal bloating) [6]. GERD often manifests with vomiting, rumination, regurgitation, and respiratory signs, and may be associated with unexplained weight loss [6]. Constipation is also prevalent in patients with RTT, and its diagnosis may be complicated in children with communication deficits, who may not be able to communicate their discomfort [6]. Abdominal bloating is associated with altered breathing patterns, abdominal distension, and pain [6]. Patients with RTT may also develop chewing or swallowing difficulties that pose a risk of aspiration of food [7]. In those patients who experience poor weight gain because of GI symptoms, a gastrostomy button may be required to maintain growth [7].

Although clinical guidelines for the diagnosis and management of GI manifestations of RTT exist [6,7], the burden of these symptoms on patients and their caregivers remains considerable. In a recent publication describing the development of a bespoke patient-reported outcomes tool for assessment of GI health in patients with RTT, parents of girls and young women with RTT reported significantly higher burden of all GI symptoms assessed, as well as more parental concerns in relation to GI issues, compared with parents of unaffected children [8]. These results highlight the adverse impact that GI manifestations have on the lives of patients with RTT and their families.

The aim of the present study was to describe the population prevalence of GI manifestations of RTT and the associated medical costs in pediatric and adult patients with RTT in the USA based on an analysis of health insurance claims data and a survey of physicians experienced in treating patients with RTT. The results of this study will improve the general understanding of RTT as a rare disease, with a focus on its important GI symptoms which contribute to patient and caregiver burden and potentially affect survival.

Materials & methods

Data sources

The study included two data source components, an insurance claims database analysis, and a physician survey. Administrative claims data from IQVIA™ Medical Claims Data (Dx) were used to describe the demographic and clinical characteristics of girls and women diagnosed with RTT, the frequency of common GI manifestations, and

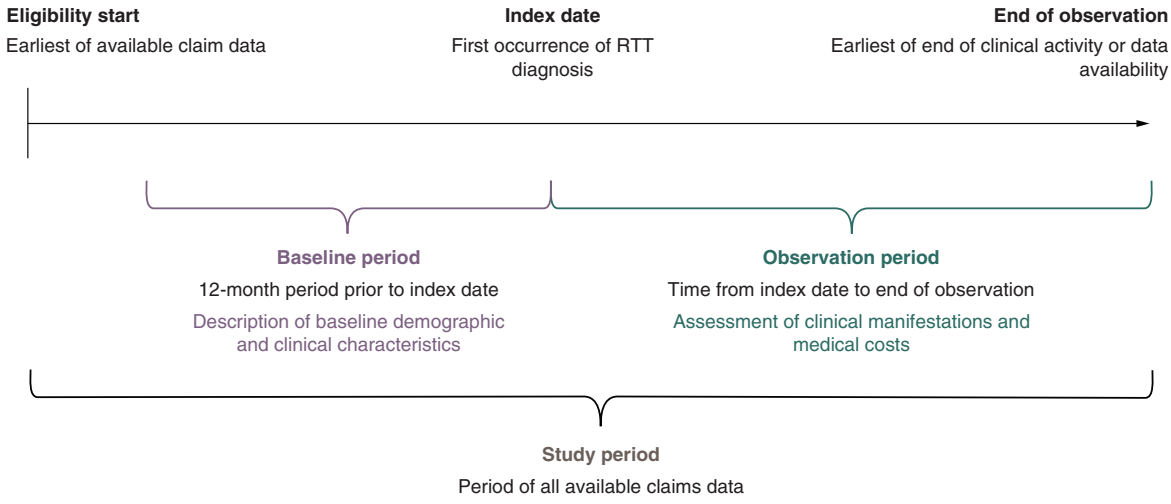

Figure 1. Design of the IQVIA™ Dx claims database study.

the associated healthcare costs. The IQVIA Dx database includes claims data from over 130 million beneficiaries, representing diverse geographic areas, employers, providers, therapy areas, and payers across the US.

The claims data analysis was supplemented with information on the prevalence of GI manifestations, treatment goals, and management of GI symptoms obtained from a cross-sectional survey of US physicians experienced in RTT management.

Methodology of the IQVIA Dx claims database analysis

Study design & eligibility criteria

A retrospective, longitudinal cohort study was conducted from 1 November 2016 to 31 October 2019.

Female patients with one or more medical claims with a primary or secondary diagnosis code for RTT (ICD-10-CM: F84.2) were included. A record of *MECP2* genetic mutation was not required for inclusion in the study. The date of the first observed diagnosis of RTT was defined as the index date. Patients aged one year or older were required to have ≥12 months of continuous enrolment prior to the index date. The 12-month period prior to the index date was defined as the baseline period and served to describe demographics and clinical characteristics. Patients with one or more medical claims for cerebrovascular disease (ICD-10-CM: I60–I69) or brain trauma (ICD-10-CM: S06) were excluded.

The observation period spanned the time from the index date until the end of clinical activity or the end of data availability (whichever occurred first). GI manifestations and healthcare costs were evaluated during the observation period. An overview of the study design is provided in Figure 1.

Outcomes of interest

Key outcomes reported in the study were the prevalence of GI manifestations of RTT and medical costs associated with GI management, including a breakdown of costs by service setting (inpatient, emergency department [ED], outpatient, home/hospice care, therapeutic services, medical supplies, durable medical equipment, other, missing).

The following GI manifestations were evaluated in the analyses: constipation, gall bladder dysfunction (including biliary tract disorders), growth abnormalities (i.e., underweight, short stature), GERD, gastroparesis, vomiting/regurgitation, and diarrhea. The list of specific ICD-10-CM codes used to identify the GI manifestations of RTT is provided in Supplementary Table 1.

Other variables of interest

Demographics and key baseline characteristics were reported. These included information on *MECP2* genetic testing (Supplementary Table 2 for a list of procedure codes used to identify the *MECP2* testing), comorbidity burden measured using the Quan-Charlson Comorbidity Index [9] (Supplementary Table 3 for a list of ICD-10-CM codes used to calculate the index), and differential diagnoses received prior to an RTT diagnosis [10,11] (Supplementary Table 4 for a list of ICD-10-CM codes used to identify potential differential diagnoses of RTT).

Statistical analysis

The prevalence of GI manifestations was described during the observation period as the frequency and proportion of patients with each GI manifestation. Mean medical costs were reported per patient per year (PPPY) to account for varying lengths of follow-up and inflation-adjusted to 2021 US dollars.

Baseline patient characteristics, prevalence of RTT manifestations, and medical costs were described for the overall study sample and for subgroups stratified by age category (pediatric patients aged <18 years vs adults aged ≥18 years). Continuous variables were summarized using means and standard deviations (SDs), and medians and interquartile ranges (IQRs). Categorical variables were summarized using relative frequencies and proportions.

Data were analyzed in SAS Enterprise Guide version 7.1 (SAS Institute, NC, US). All analyses were descriptive and no statistical comparisons between adult and pediatric groups were performed.

Methodology of the physician survey

The claims data analysis was supplemented with information on the prevalence of GI manifestations, management strategies, and treatment goals obtained from a cross-sectional, web-based survey that enrolled 100 neurologists, pediatric neurologists, or pediatricians practicing in the US who had treated two or more patients with RTT (male or female) at any time, including at least one patient in the past 2 years. Given that RTT is predominantly diagnosed among females, physicians who had seen an unexpectedly high number (i.e., ≥2) or proportion (i.e., ≥20% of cases) of male individuals with RTT were excluded. The participant sample was derived from a large panel of registered physicians practicing in a wide range of geographic locations in the US.

The survey was designed to capture a broad range of data on RTT burden and management, including that pertaining to GI manifestations. Only data related to GI manifestations are presented in this manuscript.

The survey instrument was developed based on findings from semi-structured qualitative interviews with five physicians experienced in treating patients with RTT. Several measures were taken to ensure appropriate quality of the data derived from the survey, including stress-testing and consistency checks of the survey instrument, a pre-test, in which three physicians completed the survey in the presence of a moderator to assess the understandability of the questions, with survey optimization undertaken following this phase and a pilot launch, during which data from the first few physicians completing the survey were evaluated for completeness and quality.

Survey data was collected in a single database and cleaned. Missing values were coded appropriately. The respondents were stratified by specialty (neurologists vs pediatricians). For both specialties, data were summarized descriptively using frequencies and proportions for categorical variables, and means, SDs, medians, and IQRs for continuous variables. The analyses were performed in SAS Enterprise Guide version 7.1 (SAS Institute).

Results

Participant characteristics

Data on 5940 eligible female patients with RTT including 3078 (51.8%) pediatric patients and 2862 adult patients (48.2%) were analyzed. Their baseline demographics and clinical characteristics are presented in Table 1. Mean age at index date was 20.0 years (SD: 14.5 years). All four mainland US regions were well represented in the patient sample. Medicaid (27.3%) was the most common pre-specified insurance plan type.

A total of 963 patients (16.2% of the total sample, including 613 [19.9%] pediatric patients and 350 [12.2%] adult patients) received a differential diagnosis prior to their RTT diagnosis. Among pediatric patients, the most common differential diagnoses were nonspecific developmental delay (9.2%) and autism spectrum disorder (8.7%), while cerebral palsy (8.5%) was the most common differential diagnosis in adult patients.

The frequency of *MECP2* genetic testing prior to an RTT diagnosis was low in the overall cohort, with only 69 patients (1.2%) tested. However, testing was more common in the youngest age groups, reaching 6.7% in children aged 0–4 years and 1.5% in those aged 5–10 years, compared with only 0.2% in adolescents aged 11–17 years and 0.3% in adults.

Prevalence of GI manifestations of RTT

GI manifestations were present in 2554 patients (43.0% of the overall sample), and their prevalence was slightly higher in pediatric patients (n = 1404; 45.6%) relative to adult patients (n = 1150; 40.2%, respectively). The prevalence of GI manifestations overall and by age subgroup is presented in Table 2. The most common GI manifestations in the overall cohort of patients were constipation (26.0%), GERD (18.2%), vomiting/regurgitation (10.7%), and diarrhea (5.7%).

Table 1. Baseline demographics and clinical characteristics of patients with Rett syndrome.

Characteristics	Overall cohort (n = 5940)	Age 0–4 (n = 612)	Age 5–10 (n = 1194)	Age 11–17 (n = 1272)	Pediatric (age <18; n = 3078)	Adult (age ≥18; n = 2862)
Age at index date, years						
Mean (SD)	20.0 (14.5)	2.9 (1.0)	7.5 (1.7)	13.9 (1.9)	9.2 (4.6)	31.6 (12.5)
Median (IQR)	17.0 (9–28)	3.0 (2–4)	8 (6–9)	14 (12–16)	9.0 (5–13)	29.0 (22–37)
Region, n (%)						
South	2051 (34.5)	234 (38.2)	461 (38.6)	460 (36.2)	1155 (37.5)	896 (31.3)
West	1373 (23.1)	143 (23.4)	270 (22.6)	303 (23.8)	716 (23.3)	657 (23.0)
Midwest	1328 (22.4)	124 (20.3)	252 (21.1)	272 (21.4)	648 (21.1)	680 (23.8)
Northeast	1151 (19.4)	109 (17.8)	204 (17.1)	225 (17.7)	538 (17.5)	613 (21.4)
Other[†]	4 (0.1)	1 (0.2)	1 (0.1)	0 (0.0)	2 (0.1)	2 (0.1)
Unknown/unspecified	33 (0.6)	1 (0.2)	6 (0.5)	12 (0.9)	19 (0.6)	14 (0.5)
Insurance plan type, n (%)						
Medicaid	1621 (27.3)	117 (19.1)	333 (27.9)	408 (32.1)	858 (27.9)	763 (26.7)
Commercial	1101 (18.5)	154 (25.2)	264 (22.1)	257 (20.2)	675 (21.9)	426 (14.9)
Medicare/Medicaid Dual Eligible	895 (15.1)	110 (18.0)	218 (18.3)	200 (15.7)	528 (17.2)	367 (12.8)
Medicare	665 (11.2)	8 (1.3)	5 (0.4)	6 (0.5)	19 (0.6)	646 (22.6)
Unknown/unspecified plan[‡]	1658 (27.9)	223 (36.4)	374 (31.3)	401 (31.5)	998 (32.4)	660 (23.1)
Quan-CCI[§], mean ± SD [median]	0.1 ± 0.4 [0.0]	0.1 ± 0.3 [0.0]	0.1 ± 0.3 [0.0]	0.1 ± 0.3 [0.0]	0.1 ± 0.3 [0.0]	0.1 ± 0.5 [0.0]
MECP2 genetic testing[§,¶], n (%)	69 (1.2)	41 (6.7)	18 (1.5)	2 (0.2)	61 (2.0)	8 (0.3)
Differential diagnosis of RTT[§], n (%)						
Any differential diagnosis	963 (16.2)	204 (33.3)	226 (18.9)	183 (14.4)	613 (19.9)	350(12.2)
Autism spectrum disorder	367 (6.2)	71 (11.6)	128 (10.7)	70 (5.5)	269 (8.7)	98 (3.4)
Cerebral palsy	413 (7.0)	26 (4.2)	59 (4.9)	86 (6.8)	171 (5.6)	242 (8.5)
Nonspecific developmental delay	321 (5.4)	148 (24.2)	86 (7.2)	50 (3.9)	284 (9.2)	37 (1.3)
Angelman syndrome	2 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.1)	0 (0.0)
Other childhood disintegrative disorder	6 (0.1)	0 (0.0)	0 (0.0)	3 (0.2)	3 (0.1)	3 (0.1)

[†]Includes Puerto Rico, Virgin Islands and Guam.
[‡]Includes medical claims associated with an unspecified plan, unknown third party, cash, claims processing, or missing.
[§]Evaluated during the baseline period, including the index date.
[¶]Identified using CPT codes: 81302–81304, 0234U, 81470, 81471, 81479.
CPT: Current procedural terminology; IQR: Interquartile range; Quan-CCI: Quan–Charlson comorbidity index; SD: Standard deviation.

Table 2. Prevalence of GI manifestations in patients with Rett syndrome.

	Overall cohort (n = 5940)	Age 0–4 (n = 612)	Age 5–10 (n = 1194)	Age 11–17 (n = 1272)	Pediatric (age <18; n = 3078)	Adult (age ≥18; n = 2862)
GI manifestations, any	2554 (43.0)	284 (46.4)	557 (46.6)	563 (44.3)	1404 (45.6)	1150 (40.2)
Constipation	1543 (26.0)	153 (25.0)	347 (29.1)	352 (27.7)	852 (27.7)	691 (24.1)
GERD	1079 (18.2)	121 (19.8)	215 (18.0)	257 (20.2)	593 (19.3)	486 (17.0)
Vomiting/regurgitation	636 (10.7)	115 (18.8)	152 (12.7)	128 (10.1)	395 (12.8)	241 (8.4)
Diarrhea	340 (5.7)	47 (7.7)	79 (6.6)	63 (5.0)	189 (6.1)	151 (5.3)
Growth abnormalities	315 (5.3)	49 (8.0)	102 (8.5)	83 (6.5)	234 (7.6)	81 (2.8)
Gall bladder dysfunction	118 (2.0)	0 (0.0)	5 (0.4)	20 (1.6)	25 (0.8)	93 (3.2)
Biliary tract disorders	105 (1.8)	0 (0.0)	4 (0.3)	19 (1.5)	23 (0.7)	82 (2.9)
Gastroparesis	92 (1.5)	12 (2.0)	19 (1.6)	21 (1.7)	52 (1.7)	40 (1.4)

Data are presented as n (%).
GERD: gastro-esophageal reflux disease; GI: gastrointestinal.

All GI manifestations except for gall bladder dysfunction and biliary tract disorders were slightly more prevalent in pediatric relative to adult patients with RTT (Table 2). No patients with gall bladder dysfunction or biliary tract disorders were identified in the youngest age group analyzed (aged 0–4 years) and the prevalence of these

Table 3. Medical costs of managing GI manifestations.

	Overall cohort (n = 5940)	Age 0–4 (n = 612)	Age 5–10 (n = 1194)	Age 11–17 (n = 1272)	Pediatric (age <18; n = 3078)	Adult (age ≥18; n = 2862)
GI manifestations, any	$4473 ± 27,286	$5221 ± 33,781	$4761 ± 18,672	$6337 ± 44,051	$5530 ± 34,315	$3341 ± 16,679
Constipation	$923 ± 7552	$864 ± 7527	$1261 ± 9572	$835 ± 5248	$1010 ± 7605	$830 ± 7495
GERD	$2630 ± 23,424	$1651 ± 8748	$2854 ± 14,393	$4678 ± 42,995	$3468 ± 30,202	$1732 ± 12,560
Vomiting/regurgitation	$268 ± 3993	$512 ± 4566	$213 ± 1334	$397 ± 7240	$342 ± 5212	$189 ± 1977
Diarrhea	$89 ± 1614	$139 ± 3383	$36 ± 249	$76 ± 802	$70 ± 1458	$110 ± 1765
Growth abnormalities	$252 ± 3014	$397 ± 4374	$436 ± 4458	$296 ± 2135	$368 ± 3605	$128 ± 2206
Gall bladder dysfunction	$158 ± 2620	$0.00 ± 0.00	$77 ± 1638	$106 ± 2167	$77 ± 1774	$245 ± 3290
Biliary tract disorders	$150 ± 2582	$0.00 ± 0.00	$77 ± 1638	$103 ± 2160	$76 ± 1770	$228 ± 3232
Gastroparesis	$415 ± 10,379	$1886 ± 31,359	$195 ± 3149	$261 ± 4216	$492 ± 12,970	$332 ± 6550

Data are presented as mean cost PPPY ± SD.
GERD: gastro-esophageal reflux disease; GI: gastrointestinal; PPPY: per patient per year; SD: standard deviation.

GI manifestations increased with patient age. The prevalence of gall bladder dysfunction increased from 0.4% in patients aged 5–10, to 1.6% in patients aged 11–17, and to 3.2% in adults. For biliary tract disorders the corresponding proportions for these age groups were 0.3%, 1.5%, and 2.9%, respectively.

Conversely, the prevalence of vomiting/regurgitation declined with increasing age, from 18.8% in infants and young children aged 0–4 years to 12.7% in children aged 5–10 years, 10.1% in adolescents aged 11–17 years, and 8.4% in adults. Growth abnormalities were also most frequently diagnosed in younger children aged 0–4 years (8.0%) and 5–10 years (8.5%), and less frequently in adolescents (6.5%) and adults (2.8%).

Medical costs

The mean medical cost of managing GI manifestations was $4473 PPPY (SD: $27,286) and numerically higher in pediatric patients relative to adult patients ($5530 and $3341 PPPY, respectively). In terms of the costs associated with the management of specific GI manifestations (Table 3), mean medical costs were lower in adult patients than in pediatric patients for all GI manifestations except for gall bladder dysfunction or biliary tract disorders (consistent with their lower prevalence in pediatric patients, see Table 2) and diarrhea. The mean medical costs of diarrhea management were highest in children aged 0–4 years ($139 PPPY) followed by adults ($110 PPPY).

GERD was associated with the highest mean medical cost ($2630 PPPY), of which the largest component was the cost of therapeutic services (including physical therapy, hydrotherapy, occupational therapy, speech therapy, and feeding assistance), which amounted to $1071 PPPY (SD: $8264). The mean cost of GERD was higher in pediatric ($3468 PPPY) than adult ($1732 PPPY) patients, with the largest cost observed in adolescents aged 11–17 years ($4678 PPPY) (Table 3).

The second most costly manifestation to manage was constipation ($923 PPPY), which mean cost PPPY was higher in pediatric than adult patients ($1010 vs $830, respectively). The two most prominent cost components of the overall constipation cost included inpatient ($253 PPPY, SD: $2837) and ED ($239 PPPY, SD: $3786) costs.

GI symptom prevalence & their real-world management in the physician survey

This physician survey included 100 physicians practicing in the US, of whom 51 were neurologists (including 25 pediatric neurologists) and 49 were pediatricians. The mean duration of clinical experience in the specialty (post-residency) was 17.1 (SD: 8.4) years among neurologists and 21.6 (SD: 9.2 years) among pediatricians. Survey respondents practiced predominantly in private practices (15 [29.4%] neurologists and 33 [67.3%] pediatricians), academic or university medical centers (22 [43.1%] neurologists and 7 [14.3%] pediatricians) and community-based hospitals (9 [17.6%] neurologists and 3 [6.1%] pediatricians). The mean number of patients with RTT treated by survey respondents in the past two years was 10.8 (SD: 15.3) among neurologists and 2.5 (SD: 2.4) among pediatricians.

Depending on patients' age category, 36.4%–42.3% of neurologists reported observing constipation in more than a quarter of their patients with RTT who were aged <20 years, compared with 37.8% reporting that they observed it in over a quarter of patients with RTT aged ≥20 years (Figure 2). The corresponding figures for pediatricians were 45.8%–60.0% in patients aged <20 years and 33.3% in patients aged ≥20 years, although only 15 out of 49 pediatricians (30.6%) provided information for adult patients aged ≥20 years. The pattern of

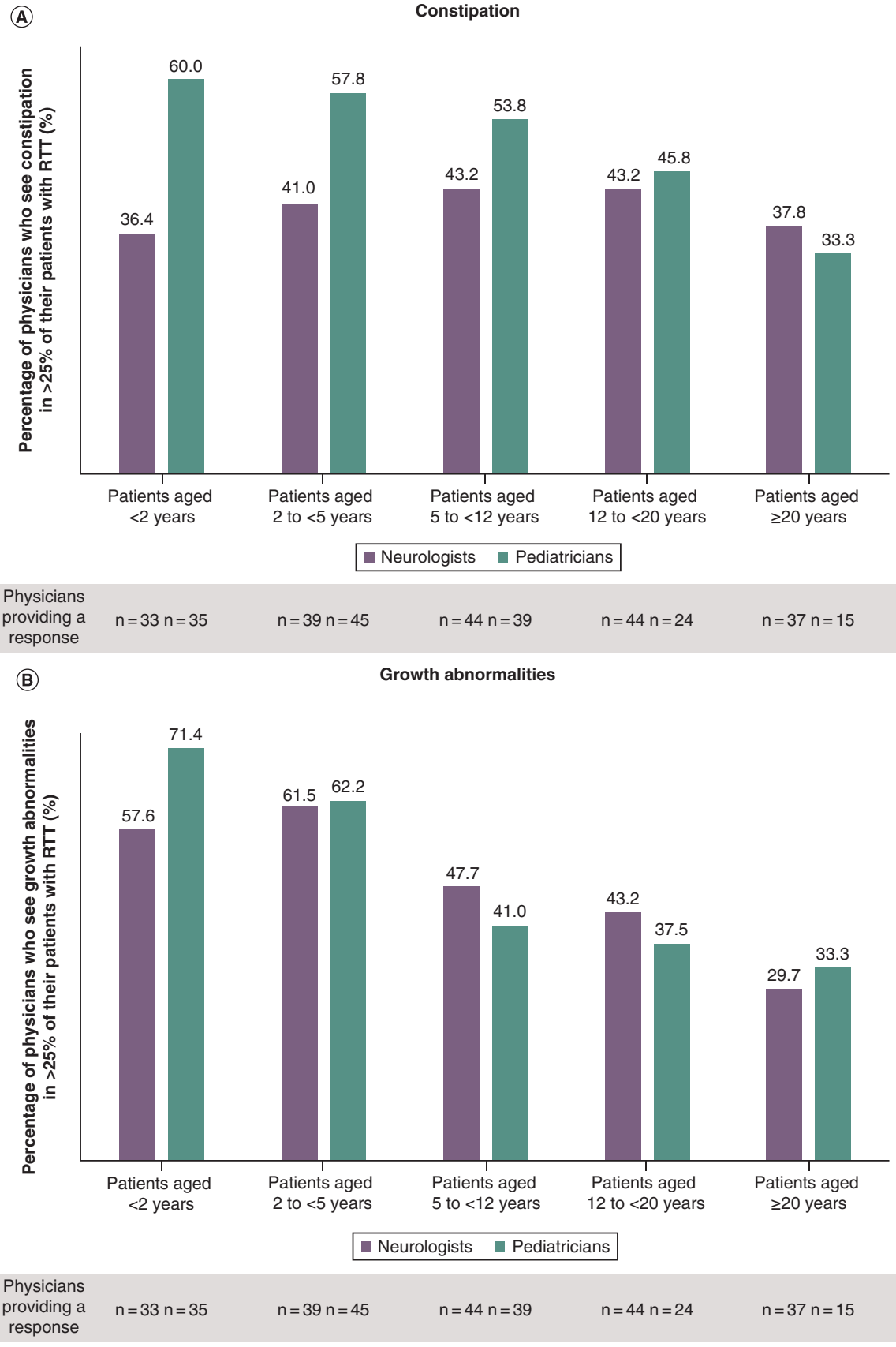

Figure 2. Proportion of surveyed physicians observing selected gastrointestinal manifestations in >25% of their patients, by physician specialty (among physicians experienced in treating a given age category). (A) Constipation. **(B)** Growth abnormalities. **(C)** Gastro-esophageal reflux disease.

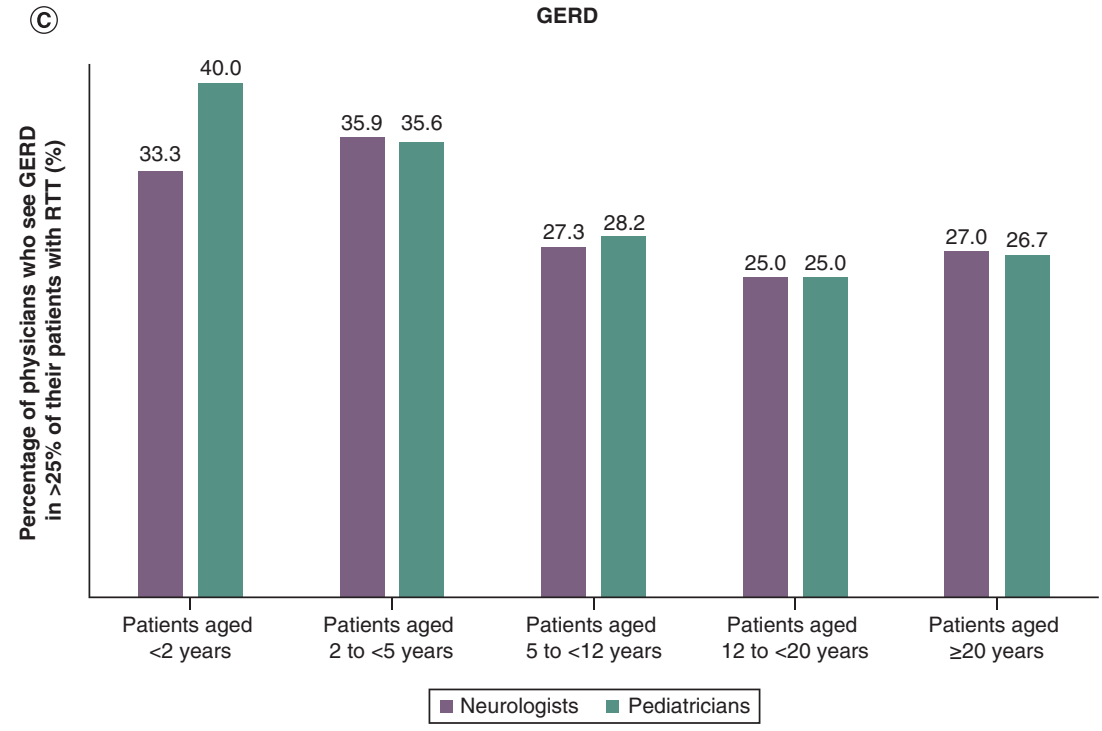

Figure 2. Proportion of surveyed physicians observing selected gastrointestinal manifestations in >25% of their patients, by physician specialty (among physicians experienced in treating a given age category) (cont.). (A) Constipation. **(B)** Growth abnormalities. **(C)** Gastro-esophageal reflux disease.

responses was generally similar for the other two GI manifestations included in the survey, GERD and growth abnormalities, with pediatricians reporting a higher prevalence of GI complications than neurologists among the younger patient groups (Figure 2).

Management of GI issues was ranked among the five most important treatment goals by 3 (5.9%) neurologists and 4 (8.2%) pediatricians surveyed. However, when asked about treatment goals from the patients' and caregivers' perspective, 8 (15.7%) neurologists and 7 (14.3%) pediatricians ranked GI symptom management among the five most important treatment goals.

Real-world management of three GI symptoms (constipation [n = 30 responses: 7 from neurologists and 23 from pediatricians], growth abnormalities [n = 20 responses: 3 from neurologists and 17 from pediatricians] and GERD [n = 11 responses: 1 from neurologists and 10 from pediatricians]), was assessed and the management of all three relied heavily on nutritional advice. For the treatment of constipation, neurologists most commonly referred patients to a dietician or to a gastroenterologist (57.1% each), while pediatricians were most likely to provide dietary recommendation (91.3%), refer to a dietician (78.3%), and prescribe laxatives (69.6%). Management of growth abnormalities most commonly involved monitoring patient's weight, heigh, and body mass index (n = 3 [100%] neurologists and n = 14 [82.4%] pediatricians). Other common management approaches included providing dietary recommendations and referral to a dietician (both selected by 1 [33%] neurologist and 13 [76.5%] pediatricians), and recommending supplements (1 [33%] neurologist and 10 [58.8%] pediatricians). With regards to GERD, the single neurologist who provided a response stated they recommended anti-reflux medications, referred to a dietician, provided dietary recommendations/guidance, and recommended the placement of a gastrostomy tube. Among the 10 pediatricians who responded, all (100%) prescribed anti-reflux medication, 8 (80%) referred to a dietician, and 7 (70%) provided dietary recommendations and advice.

Discussion

This study is, to the authors knowledge, the first to describe the medical costs associated with GI symptoms of RTT, as well as provide up-to-date estimates of GI symptom prevalence from two separate sources. In the sample of nearly 6000 patients with RTT, GI manifestations were common, affecting 43% of all patients. The most prevalent GI manifestations included constipation, GERD, vomiting/regurgitation, and diarrhea. The prevalence and nature of GI manifestations that patients with RTT experienced changed with age. For most GI manifestations, prevalence was slightly higher in pediatric patients relative to adult patients, except for biliary tract disorders and gall bladder dysfunction, which were rarely observed in patients younger than 11 years of age. Conversely, the prevalence of vomiting/regurgitation and growth abnormalities declined notably with increasing age. For constipation, GERD, diarrhea, and gastroparesis, prevalence was broadly similar across all age groups.

The results from the physician survey differed somewhat from those obtained from the analysis of the IQVIA Dx database. Physicians reported observing constipation and GERD less frequently in adult patients, whereas database-derived prevalence of constipation and GERD varied little between age groups. This was largely driven by the responses from pediatricians, who more frequently reported observing GI symptoms of RTT in younger patient groups, which suggests they may be more attuned to non-neurologic symptoms of RTT than neurologists.

The prevalence of GI manifestations in this study was somewhat lower than reported in the literature. In a survey of 983 parents of girls and women with RTT registered in the International Rett Syndrome Foundation North American RTT database, the overall prevalence of GI dysmotility (which included GERD, gastroparesis, vomiting/regurgitation, night-time awakening with irritability, constipation, straining with bowel movements, passage of hard stools) was 92%, compared with 43% in our study [12]. The prevalence of constipation in the current study was 26%, compared with 56–80% reported in North American [12] and UK [13] parent surveys, and 76–87% in Australian and international RTT databases [3]. Similarly, the prevalence of GERD in the literature has been reported at 15.3–39% [3,12], compared with 18.2% in our study. This discrepancy is likely to be related to different study designs, with surveys or population-based databases relying on parent-reported symptoms, whereas our analysis only captured those manifestations that required a healthcare encounter.

In terms of medical costs, GERD was associated with higher mean medical costs PPPY than the other GI manifestations evaluated in the present study. It should, however, be noted that the SDs associated with mean medical costs were large, suggesting wide variability in the costs of the GI manifestations assessed. While we have identified no studies reporting specifically on the costs of managing GI manifestations in RTT, in an analysis of the Australian Rett Syndrome Database, mean healthcare costs associated with RTT management overall were estimated at AUD 21,158 PPPY (equivalent to USD 25,691 as of December 2022 [14,15]), and ranged from AUD 238 to AUD 85,776 (equivalent to USD 289 to USD 104,151 [14,15]) [16], also suggesting substantial between-patient variability in the healthcare costs incurred. Given the variability in healthcare costs among patients with RTT, future studies could investigate the association between specific patient characteristics and healthcare resource utilization and costs, both in relation to the management of GI manifestations and other aspects of care for patients with RTT. Such an analysis would enable identifying those patients with RTT who potentially have the highest unmet medical need in terms of symptom management.

Although comprehensive guidelines on the management of GI manifestations in RTT exist [6,7], GI manifestations were rarely perceived by physicians as an important treatment goal in the present study and their real-world management relied primarily on nutritional advice. While this should be viewed in light of other severe and prevalent symptoms of RTT, such as scoliosis, limited ambulation, and epilepsy [3], the results of this study call for increased awareness toward GI manifestations of RTT and increased efforts to maximize symptom relief with optimal management. Previously published literature recommends that, where possible, patients with RTT should receive care from a dedicated multidisciplinary team, which could optimize the management of the complex symptoms and comorbidities associated with RTT [17].

The strengths of this study included supplementing the IQVIA Dx database analysis with results from a carefully designed physician survey, which allowed physician perceptions of GI symptoms in RTT to be captured along with findings regarding GI manifestations and associated costs based on claims data. The combination of the IQVIA Dx database and a physician survey means that the prevalence and burden of GI manifestations could be captured across two independent data sources, adding credibility to the study results. The study further benefited from large sample sizes that were diverse in terms of geographic area (both data sources), insurance type (IQVIA Dx analysis), and physician specialty (physician survey).

With regards to study limitations, the database analysis relied on completeness and accuracy of data entered into the IQVIA Dx database. In particular, errors in medical claim coding could result in misclassification of RTT diagnosis, GI manifestations, and associated costs. Furthermore, the prevalence of GI manifestations was likely underestimated in the IQVIA Dx database analysis due to the fact only those symptoms which required a healthcare encounter were captured, and the reliance on coding of physician encounters with a GI symptom specifically. Future studies utilizing alternative data sources, such as caregiver surveys or institutional electronic health records, could supplement the current study and help to provide a more complete picture of GI symptom prevalence. The physician survey component of this study relied on physicians' report of past experiences associated with treating patients with RTT and may be subject to errors in physicians' recollection of these experiences. This is particularly relevant given the rarity of RTT and the resulting relatively low patient numbers that survey respondents treated. Finally, as our study was set in the US, its results may not be reflective of the burden and management of GI symptoms of RTT in other countries.

Conclusion

GI issues are a well-known, common manifestation of RTT. Insurance claims data and physician perspectives suggest that both pediatric and adult patients with RTT experience a high burden of GI manifestations, which are also associated with considerable medical costs. Proactively addressing GI manifestations is achievable as a component of existing standard of care for patients with RTT. However, despite the clinical and financial burden of GI manifestations in RTT, their management remains under-represented as an RTT treatment goal among the treating physicians, warranting increased attention toward GI symptoms in day-to-day care of patients with RTT and strengthening the efforts to maximize symptom relief with optimal management.

Summary points

- This study combined an insurance claims database analysis and a cross-sectional, web-based survey of 100 US physicians (51 neurologists and 49 pediatricians) experienced in Rett syndrome (RTT) management to quantify the burden of gastrointestinal (GI) manifestations among patients with RTT.
- GI manifestations affected 43.0% of all patients and the most common GI manifestations were constipation (26.0%), gastro-esophageal reflux disease (18.2%), vomiting/regurgitation (10.7%), and diarrhea (5.7%).
- All GI manifestations except for gall bladder dysfunction and biliary tract disorders were slightly more prevalent in pediatric relative to adult patients with RTT.
- The mean medical cost of managing GI manifestations was $4473 PPPY and numerically higher in pediatric relative to adult patients with RTT ($5530 and $3341 PPPY, respectively).
- Mean medical costs were numerically lower in adult patients than pediatric patients for all GI manifestations except for gall bladder dysfunction or biliary tract disorders (consistent with their lower prevalence in pediatric patients) and diarrhea.
- Management of GI manifestations was ranked among the five most important treatment goals by 3 (5.9%) of surveyed neurologists and 4 (8.2%) of pediatricians when considered from the physician perspective and by 8 (15.7%) and 7 (14.3%), respectively, when considered from the patient and caregiver perspective.
- While GI issues are a well-known, common manifestation of RTT, insurance claims data and physician perspectives suggest that both pediatric and adult patients with RTT experience a high burden of GI manifestations, which translate to important medical costs.
- Despite the considerable clinical and financial burden of GI manifestations in RTT, management of GI manifestations remains under-represented as an RTT treatment goal among treating physicians.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://bpl-prod.literatumonline.com/doi/10.57264/cer-2023-0054

Author contributions

DM May, JM Youakim, V Abler, WY Cheng, K Kponee-Shovein and A Satija conceptualized and oversaw the research. J Neul and JE Piña-Garza provided expert clinical advice on research design, execution, and manuscript development. KKS, AS, MM, ND, KS, NL, and AB performed the analyses. K Kponee-Shovein, A Satija, P Lefebvre and WY Cheng provided senior oversight over data analysis. All authors contributed to the development of the manuscript and approved its final version for publication in the Journal of Comparative Effectiveness Research.

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Competing interest disclosure

DM May, V Abler and JM Youakim are employees and option/shareholders of Acadia Pharmaceuticals Inc. J Neul has served as a consultant or advisor for Alcyone, the Analysis Group, Medscape, NeuroGene, Ovid, Peer Review Institute, Roche, Signant, and Taysha and is an option/shareholder of Acyone and LizarBio. JE Piña-Garza has served as a consultant, speaker, or advisor for the Analysis Group, Aquestive, Eisai, Neurelis, SK, Life Sciences, Sunovion, Supernus, and UCB. K Kponee-Shovein, A Satija, M Mahendran, N Downes, N Lema, A Boca, P Lefebvre, and WY Cheng are employees of Analysis Group, Inc., which received funding from Acadia Pharmaceuticals Inc. to conduct this study. K Sheng was an employee of Analysis Group at the time of the study, which received funding from Acadia Pharmaceuticals Inc. to conduct this study. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

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Ethical conduct of research

No informed consent was required for the analysis of the IQVIA Dx database due to the de-identified nature of the data. For the physician survey study, the study protocol was approved by Pearl Institutional Review Board (approval no. 21-ANGR-104). All participants in the physician survey provided their informed consent to participate in the study.

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