Risk Factors Associated with Aspiration Outcomes in Patients with Rett Syndrome: Analysis of Real-World Data in the United States

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BACKGROUND

- Rett syndrome (RTT) is a rare neurodevelopmental disorder affecting 7.1 in 100,000 live female births and the leading cause of intellectual disability among young females.^{1,2}
- RTT syndrome is associated with multisystem comorbidities that contribute to overall healthcare utilization and mortality.^{3,4}
- The top three causes of mortality among individuals with RTT are respiratory conditions: lower respiratory tract infection [LRTI] (37%), aspiration and/or asphyxiation (32%), and respiratory failure (14%).⁴
- Aspiration events can often be silent or unwitnessed, along with frequent respiratory disturbances which can complicate the diagnosis process.^{5,6}
- Respiratory manifestations such as aspiration and associated predictors related to aspiration are not fully known; thus, real-world data analysis was conducted to examine risk factors associated with aspiration among incident RTT patients in the United States.

OBJECTIVE

 To examine risk factors associated with aspiration among incident RTT patients in the United States.

METHODS

Study Design, Population & Measures

- A retrospective medical and pharmacy claims analysis from 8/1/2020 to 3/31/2023 using IQVIA APLD (Anonymized Patient Level Data) database was performed.
- Newly diagnosed (incident) RTT (ICD-10-CM: F84.2) patients between 2/1/2021 to 3/31/2022 (index date) with continuous enrollment in the 6-month pre-index and 12 months post index period were selected.
- Any patient with a claim for cerebrovascular disease or brain trauma during study period were excluded.
- Study measures included baseline (pre-index) demographic (e.g., age, gender) and clinical comorbidities (e.g., cough, LRTI, dysphagia, neurological disorders) as well as occurrence of postindex aspiration, based on ≥1 claim for ICD-10-CM diagnosis codes (J69.0, J69.8, Y84.4).

Statistical Analysis

- A single-factor (unadjusted) logistic regression analysis was conducted, with aspiration as the dependent variable and baseline clinical/demographic variables as independent variables, to identify predictors associated with aspiration at follow-up.
- Subsequently, a backward selection logistic regression was used to identify potential list of baseline
 predictors of aspiration occurrence during post-index; with post-index aspiration as the dependent
 variable and age, gender, and 13 baseline comorbidities as independent variables.
- A final adjusted multivariable model, including age, gender, and significant baseline clinical predictors identified from the backward selection logistic regression, was run to estimate the associations between these predictors and occurrence of aspiration during post-index.

RESULTS

There were 7,418 RTT patients identified from the IQVIA APLD database. The final sample included 1,994 incident patients with RTT (Figure 1). The mean age was 21.2 \pm 17.7; 51.1% were <18yrs of age and 78.9% were female.

 A total of 145 (7.27%) patients experienced aspiration post-RTT diagnosis; with a mean time of 125±118.44 days from RTT diagnosis to incidence of aspiration.

Figure 1: Patient Selection Attrition



*Percentages was based on total RTT patients included in the final analysis

- The single-factor (unadjusted) logistic regression showed that several baseline clinical measures were strongly associated with an increased odds of aspiration (Table 1). Of note, patients with a prior history of: aspiration (OR:19.18, 95% CI: 10.8–36.49), LRTI (OR: 4.98, 95% CI: 2.79–8.91), vomiting (OR: 2.85, 95% CI: 1.36–5.97), dysphagia (OR: 4.98 (95% CI: 3.25–7.63), cough (OR: 5.00, 95% CI: 2.84–8.81), and respiratory failure (OR: 3.69, 95% CI: 2.03–6.71) among others were all independent predictors of aspiration after RTT diagnosis (Table 1).
- An exploratory stepwise logistic regression was performed using all baseline predictors (presented in Table 1), identified several baseline clinical predictors for aspiration at follow-up (figure not shown here); The results showed that previous aspiration was a significant predictor of future aspiration (OR: 9.83, 95% CI: 4.79–20.17), along with cough (OR: 3.61, 95% CI: 1.91–6.84), dysphagia (OR: 2.50, 95% CI: 1.50–4.15), and neurological disorders (OR: 1.84, 95% CI: 1.23– 2.75). LRTI was predictive but not significantly associated with aspiration (OR: 1.81, 95% CI: 0.89– 3.68).

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Table 1: Single Factor Logistic Re	egressio	on Analy	sis with	Occurr	ence of
Baseline Predictors	Aspiration Event		No Aspiration Event		Unadjusted OR (95%
	N	%	N	%	CI)
Total	145	7.27	1,849	92.73	
Age					
Pediatric (<18 years)	82	56.55%	937	50.68%	1.27 (0.90, 1.78)
Adult (≥18 years)	63	43.45%	912	49.32%	Reference
Gender					
Male	36	24.83%	378	20.44%	1.28 (0.86, 1.90)
Female	109	75.17%	1466	79.29%	Reference
Clinical comorbidities of interest					
Aspiration	23	15.86%	18	0.97%	19.18 (10.08, 36.49)
LRTI	17	11.72%	48	2.60%	4.98 (2.79, 8.91)
Respiratory failure	15	10.34%	56	3.03%	3.69 (2.03, 6.71)
Vomiting	9	6.21%	42	2.27%	2.85 (1.36, 5.97)
Cough	18	12.41%	51	2.76%	5.00 (2.84, 8.81)
Dysphagia	35	24.14%	111	6.00%	4.98 (3.25, 7.63)
Neurodevelopmental disorders	48	33.10%	388	20.98%	1.86 (1.30, 2.68)
Gastrointestinal disorders	46	31.72%	242	13.09%	3.09 (2.12, 4.49)
Growth abnormalities/ nutritional disorders	21	14.48%	106	5.73%	2.78 (1.69, 4.60)
Musculoskeletal disorders	14	9.66%	64	3.46%	2.98 (1.63, 5.46)
Neurological disorders	53	36.55%	319	17.25%	2.76 (1.93, 3.96)
Infectious/viruses	26	17.93%	134	7.25%	2.80 (1.77, 4.43)
Respiratory disorders	36	24.83%	141	7.63%	4.00 (2.64, 6.05)
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Figure 2 Backward Selection Logistic Regression for Aspiration after removing baseline Aspiration

Category P-value Adjusted OR (95% CI) LRTI 0.0110 2.34 (1.22, 4.51) 0.0001 3.39 (1.82, 6.29) Couah 3.04 (1.86, 4.99) Dysphagia 1.43 (0.90, 2.26) Gastrointestinal disorders 0.1283 1.77 (1.18, 2.66) Neurological disorders 0.0058 -20 -15 -10 -5 5 10 15 20

Abbreviations: CI=Confidence interval, LRTI=Lower respiratory tract infection; OR=Odds ratio

Figure 3 Multivariate Logistic Regression for Aspiration after removing baseline Aspiration

Neurological disorders	0.0009	-	1.93 (1.31, 2.85)
Dysphagia	<0.0001		3.44 (2.16, 5.47)
Cough	0.0001	→ —	3.45 (1.86, 6.40)
LRTI	0.0061		2.49 (1.30, 4.79)
Gender	0.7503	+	1.07 (0.70, 1.63
Age	0.2782	•	0.82 (0.57, 1.17
ategory	P-value	1	Adjusted OR (95% 0

Abbreviations: CI=Confidence interval, LRTI=Lower respiratory tract infection; OR=Odds ratio

- After removing baseline aspiration from the backward selection model, results indicated (Figure 2) that baseline LRTI (OR: 2.34, 95% CI: 1.22-4.51), cough (OR: 3.39, 95% CI: 1.82-6.29), dysphagia (OR: 3.04, 95% CI: 1.86-4.99), and neurological disorders (OR: 1.77, 95% CI: 1.18-2.66) are significant predictors of aspiration. Gastrointestinal disorders was predictive, however, did not show a significant association (OR: 1.43, 95% CI: 0.90-2.26).
- Based on the four significant baseline clinical predictors identified from backward selection, a confirmatory multivariable logistic regression was conducted including age, gender, LRTI, cough, dysphagia, and neurological disorders. The final model showed cough (OR: 345, 95% CI: 1.86–6.40; p=0.0001), dysphagia (OR: 3.44, 95% CI: 2.16–5.47; p<0.0001), LRTI (OR: 2.49, 95% CI: 1.30–4.79, p=0.0061), and neurological disorders (OR: 1.93, 95% CI: 1.31–2.85, p=0.0009), increased the odds of aspiration multifold. In contrast, age and gender were not significantly associated with aspiration (Figure 3).</p>

CONCLUSIONS

- This real-world analysis of RTT patients suggest that patients with a prior history of cough or dysphagia have a three times greater likelihood of aspiration. Similarly, patients with a history of LRTI and neurological disorders have a nearly two times greater odds of aspiration.
- Providers should monitor individuals with baseline predictive risk factors for aspiration and institute preventative measures and clinical protocols even in the absence of aspiration symptoms.

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