Adaptive behaviors over time in children and young adults with classic galactosemia

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Background

- Classic galactosemia (CG) results from an inability to metabolize galactose caused by deficiency of the enzyme galactose-1-phosphate uridylyltransferase (GALT). Infants with CG who consume high galactose milk accumulate elevated galactose metabolites and may experience multi-organ failure.[1,2]
- On a galactose-restricted diet, infants with CG survive and initially thrive, although by mid-childhood most present with developmental impairments.[1-3]
- The developmental complications prevalent among CG patients include speech, cognitive, motor, and socioemotional difficulties. These outcomes demonstrate incomplete penetrance (prevalence of clinical outcomes) and variable expressivity (degree of severity in clinical outcomes) and occur despite early detection and rigorous lifelong dietary restriction of galactose.
- Whether complications in CG progress over time remains unclear.[4,5]

Objective

- **To address whether the prevalence and severity of developmental complications experienced by patients with CG change over time using both cross-sectional and longitudinal analyses.**

Methods

- Patients ≤30 years old with CG (or parents responding on their behalf) were surveyed in a longitudinal study; unaffected siblings served as controls.
- Both cases and controls were assessed over a period of years using ≥1 of the following validated instruments: the Developmental Profile-3 (DP-3; 2014)[6], the Adaptive Behaviors Assessment System-3 (ABAS-3; 2015 to 2016)[7], and most recently, the Vineland Adaptive Behavior Scales-3[8] (VABS-3; from October 2021 to the time of study analyses in May 2022).
- Cross-sectionally, both domain-specific and composite normed standard scores (Table 1) were summarized using mean (SD) and unadjusted linear regression against age, pooled and separately by each individual measure, among cases and controls separately – allowing exploration of changes in scores on the population level.
- Longitudinally, all normed scores from patients with ≥2 measures (collected with different instruments) across time were summarized categorically into whether that aspect of function increased or decreased over time – allowing exploration of changes in scores on the individual level.

Table 1. Domains assessed via each developmental instrument

	DP-3	ABAS-3	Vineland-3
Domains	Communication	Conceptual	Communication
	Adaptive	Practical	Daily living skills
	Social-emotional	Social	Socialization
	Physical	-	Motor skills
Composite	General development score	General adaptive composite score	Adaptive behavior composite score

Results

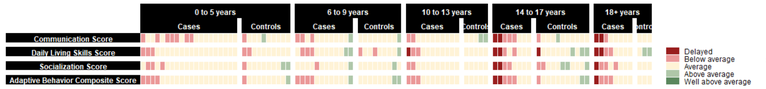
- A total of 158 cases and 84 control individuals were assessed using ≥1 of the 3 instruments (**Table 2**).

Table 2. Patients and age at the time of measure by each instrument

	DP-3		ABAS-3		Vineland-3	
	n	Mean±SD age, years	n	Mean±SD age, years	n	Mean±SD age, years
Cases (n=158)	37	8.9±1.9	103	11.9±7.1	56	9.4±6.4
Controls (n=84)	23	9.4±1.9	44	12.0±6.2	38	10.6±6.4

- As expected, normed scores from all 3 instruments showed statistically significantly higher deficit (lower scores) among cases than controls. Mean±SD composite standard scores were 76.1±15.4 (DP-3), 90.9±16.3 (ABAS-3), and 91.8±14.7 (Vineland-3) for cases; and were statistically and 99.3±14.1 (DP-3), 100.7±11.6 (ABAS-3), and 104.9±10.8 (Vineland-3) for controls. Domain-specific analyses also showed lower normed scores among cases, with the majority impacted scoring below average on more than one domain (Vineland-3 data shown **in Figure 1**; other data not shown).

Figure 1. Vineland-3 domain-specific scores among individual cases and controls, stratified by age



Cross-sectional analyses

- Linear regression analyses of cross-sectional cohorts showed that, with increasing age, normed composite (**Figure 2**) and domain-specific (data not shown) scores declined slightly among cases but not controls for ABAS-3 and Vineland-3, whereas for DP3, decline with age was observed for both cases and controls.

Longitudinal analyses

- In contrast, longitudinal analyses of normed scores for individual participants across ≥2 different instruments did not show declines for either cases or controls over time (**Table 3**).
  - Over time, when switching assessment tools, the majority of both cases (71.4%) and controls (81.0%) did not show declines over time in composite scores **(Figure 3; Table 3).**
  - For 2 of the 3 domains scored, there was a slightly higher percentage of cases than controls with declines **(Table 3).**

Figure 3. Longitudinal analysis of composite scores for cases (top; n=35) and controls (bottom; n=21)

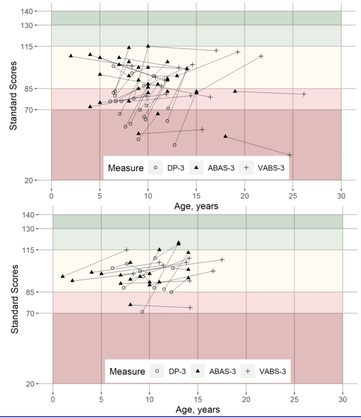
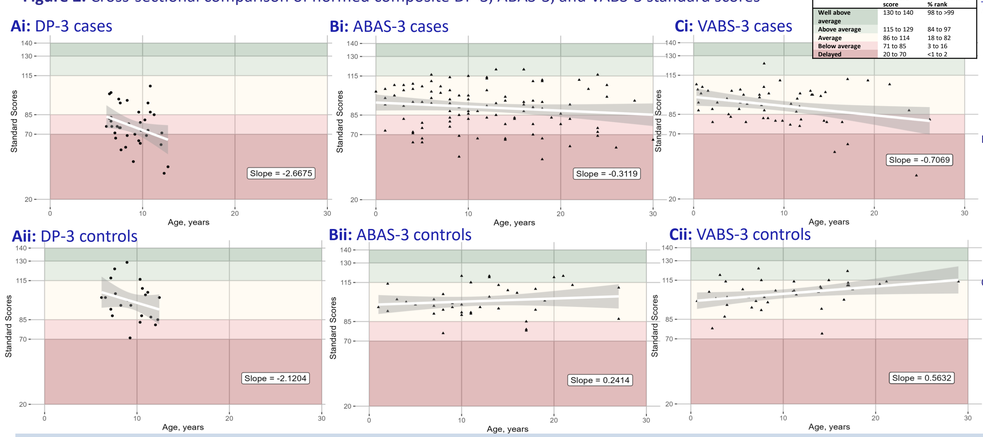


Table 3. Longitudinal analyses* in patients using ≥2 instruments

	Increase* n (%)		Decline* n (%)	
	Cases	Controls	Cases	Controls
Composite score	**23 (71.9)**	**17 (81.0)**	**9 (28.1)**	**4 (19.0)**
Communication	19 (59.4)	14 (66.7)	13 (40.6)	7 (33.3)
Adaptive	22 (68.8)	14 (66.7)	10 (31.2)	7 (33.3)
Social	20 (62.5)	16 (76.2)	12 (37.5)	5 (23.8)

*No longitudinal data available for the physical domain

Figure 2. Cross-sectional comparison of normed composite DP-3, ABAS-3, and VABS-3 standard scores



	Standard score	Corresponding % rank
Well above average	130 to 140	98 to >99
Above average	115 to 129	84 to 97
Average	86 to 114	18 to 82
Below average	71 to 85	3 to 16
Delayed	20 to 70	<1 to 2

Interpretations

A) DP-3 (scores normed for age, sex)
   i. Cases (mean±SD of 76.1±15.4): for each 1-year increase in age, there is an approximately 2.67 decrease in mean standard score
   ii. Controls (mean±SD of 99.3±14.1): for each 1-year increase in age, there is an approximately 2.12 decrease in mean standard score

B) ABAS-3 (scores normed for age, sex)
   i. Cases (mean±SD of 90.9±16.3): for each 1-year increase in age, there is an approximately 0.33 decrease in mean standard score
   ii. Controls (mean±SD of 100.7±11.6): for each 1-year increase in age, there is an approximately 0.24 decrease in mean standard score

C) VABS-3 (scores normed for age, sex)
   i. Cases (mean±SD of 91.8±14.7): for each 1-year increase in age, there is an approximately 0.71 decrease in mean standard score
   ii. Controls (mean±SD of 104.9±10.8): for each 1-year increase in age, there is an approximately 0.56 decrease in mean standard score

Discussion and future directions

- This study investigated the occurrence and change over time of several developmental deficits assessed for cases and controls.
  - While this study was not powered to study the correlation of deficits occurring across domains, we observed some evidence to suggest that patients with deficits in one domain also tended to have deficits in other domains.
  - Across all domains, while cross-sectional analyses demonstrated slightly lower normed scores among older cases with CG, suggesting some cases were falling further behind their peers over time, longitudinal analyses in which participants were evaluated using one tool and then subsequently using another, did not demonstrate worsening of deficits for individual participants over time.
  - To the limits of this study, these data suggest that even when normed to a control population, the developmental outcomes assessed did not substantially worsen with age for people with CG.
- Strengths of this study included the relatively large sample size for this rare disease and long follow-up window; as well as the use of unaffected sibling controls from the same families to help contextualize the findings, accounting for potential environmental factors and also standardizing response patterns among caregivers who completed surveys for both their affected and unaffected children.
- Key limitations included absence of repeat measures using the same instrument. Despite the 3 instruments used sharing similar constructs, their exact measurement properties and cohorts tested differed, as demonstrated by the cross-sectional decline over time in scores for controls on the DP-3 but not the VABS-3 or ABAS-3. How this limitation impacted observed trends over time is presently unclear.
- This study provides real-world evidence comparing the results of established, normed instruments, including the DP-3, ABAS-3, and Vineland-3, to better understand how people with CG score, relative to their unaffected siblings, using these instruments over time.
- These data also provide a foundation for our ongoing efforts to collect longitudinal data using the VABS-3, to allow a better understanding of prevalence and possible changes over time of developmental complications experienced by children and adults with CG.

Disclosures

JLFK, NP, and NHS have no disclosures. CQ, SMS and PJ are employees of Broadstreet HEOR, which received funds from Jaguar Gene Therapy related to this work. CW, BM and DG are employees of Jaguar Gene Therapy.

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