Progressive Worsening of Central Nervous System Phenotype in Children With Classic Galactosemia: A Cross-Sectional Analysis

Poster 504

S. Wang[1], F. Lawson[1], R. Perfetti[1], S. Shendelman[1]. Applied Therapeutics Inc.[1], New York, NY, USA.

Background

- Classic Galactosemia (CG) is a rare inborn metabolic disease caused by an autosomal recessive mutation that severely depletes galactose-1-phosphate uridylyltransferase (GALT), leading to accumulation of galactose and its metabolites, galactose-1-phosphate (Gal-1P) and galactitol.[1,2]
- Galactitol is an aberrant toxic metabolite, which is only formed in Galactosemia patients and has been shown to cause central nervous system (CNS) abnormalities in an animal model of Galactosemia.[3]
- The condition is fatal in infancy if galactose is not eliminated from the diet. For this reason, there is mandatory newborn screening in the US and other countries, followed by immediate initiation of a galactose-restricted diet.[2,4] However, despite dietary restriction, endogenous production of galactose by the body through *de novo* synthesis results in long-term complications, including impairments in neurologic, ocular, and reproductive function.[4]

Objectives and Study Design

- The objective of this study was to evaluate the age-dependent changes in the neurological and behavioral phenotype in children with classic Galactosemia adhering to a galactose-restricted diet from the perinatal period of life.
- This study was a cross-sectional analysis of baseline data of pediatric subjects recruited to participate in a pivotal trial of AT-007 (AT-007-1002). At baseline, participating children and adolescents were given tests of speech, motor function, cognition, and behavior. Data were analyzed for individual subjects and among three age groups:
  - Group 1: ≥13 to <18 years of age
  - Group 2: ≥7 to ≤12 years of age
  - Group 3: ≥2 to ≤6 years of age

Table 1: Instruments for the Study

Domain	Test	Description	Score Mean ± SD
Language	OWLS: Oral Expression Test[5]	Integrated, global approach to language assessment. The Oral Expression Scale (OES) measures expressive language, requiring the examinee to answer questions, finish sentences, and generate sentences in response to visual and oral prompts.	Standard score (adjusted for age in year and month, sex) 100 ± 15
Cognition	NIH Toolbox Cognition Battery, Total Composite[6,7]	The NIHTB-CB measures the mental processes involved in gaining knowledge and comprehension, such as thinking, knowing, remembering, judging, and problem-solving.	Age-corrected standard scores (adjusted for age) 100 ± 15
Balance	NIH Toolbox Standing Balance Test[6,8]	The subject's anterior-posterior postural sway information is fed wirelessly to an iPad. These data are converted using an item response theory (IRT) model to derive a theta score for each subject representing the relative overall balance ability or performance of the subject.	Fully corrected T-score (adjusted for gender, age, ethnicity and education differences) 50 ± 10
Dexterity	NIH Toolbox 9-hole Pegboard Dexterity Test[6,9]	Measures subject's ability to coordinate the fingers and manipulate objects in a timely manner by picking up pegs and putting them into holes and then returning the pegs to their original position.	
Behavior	BASC-3 Behavior Symptoms Index[10]	BASC-3 component used to assess attention, atypicality, and withdrawal with a 4-point parent rating scale (PRS) in which each item is rated as N for Never, S for Sometimes, O for Often, or A for Almost always.	T-score (adjusted for age); higher scores indicate more risk 50 ± 10
Adaptive Skills	BASC-3 Adaptive Skills[10]	Component of BASC-3. Uses same 4-point PRS (N for Never, S for Sometimes, O for Often, or A for Almost always) to assess adaptability, social skills, leadership, functional communications, and activities of daily living (ADLs).	T-score (adjusted for age) 50 ± 10

Results

Table 2: Baseline characteristics

Age at Entry (years)	Gender	Urine Galactitol (mM/mol/L of Urine Creatinine)	GALT Enzyme Activity (nmol/h/mg)	Gene Mutation
15	Female	161	0.1	p.Q188R
14	Female	10.6	0.4	p.K285N*
13	Female	175	0	p.Q188R
12	Male	205	0	p.Q188R
12	Female	332	0	p.Q188R, p.Q188P
12	Male	209	0	p.Q188R, p.Y209C
11	Female	259	0.1	p.Q188R
9	Male	152	0.1	p.K285N/other
9	Male	187	0	p.Q188R (Gin188Arg)
9	Female	166	0	p.Q188R, p.Y209C
8	Male	213	0.1	p.Q188R
7	Female	304	0	p.Q188R
6	Male	275	0	p.Q188R
5	Female	284	0	p.Q188R, p.Q344K
4	Male	222	0	p.Q188R, p.K285N
4	Female	441	0	p.Q188R
4	Female	241	0	p.Q188R (Gin188Arg)
4	Female	265	0	p.Q188R
3	Male	246	0	p.L95P, p.Q188R

*This patient is believed to be a "biochemical variant" patient with remaining residual GALT enzyme activity. A second allele mutation was not identified by SNP analysis for known GALT gene mutations, and enzyme activity was 0.4%, higher than the expected 0.1%. The patient did not qualify under inclusion criteria and was not randomized to the study

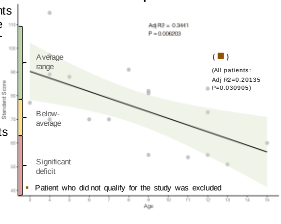
Table 3: Results Overview

Domain	Patients With Severe Impairment (Standard Scores Below 2 SD) % (n/N)		
Age Group	2–6 yo	7–12 yo	13–18 yo
Language	0.0 (0/7)	33.3 (3/9)	66.7 (2/3)
Cognition	0.0 (0/4)	75.0 (6/8)	100.0 (2/2)
Balance	0.0 (0/6)	50.0 (3/6)	66.7 (2/3)
Dexterity	42.9 (3/7)	42.9 (3/7)	66.7 (2/3)
Behavior	0.0 (0/6)	22.2 (2/9)	33.3 (1/3)
Adaptive Skills	0.0 (0/6)	0.0 (0/9)	33.3 (1/3)

Language

- All 19 children, aged 3–15 years, underwent language assessment.
  - **Younger age group** (2–6): the majority of patients (4/7; 57.1%) had a standard score in the average range (85–115); 3 patients (42.9%) had a below-average standard score (70–84), and no patient had a score in the significant delay range (<70)
  - **Intermediate age group** (7–12): the majority of patients (5/9; 55.6%) had a below-average standard score (70–84), and 3 patients (33.3%) had a score in the significant delay range (<70)
  - **Older age group** (13–15): the majority of patients (2/3; 66.7%) had a score in the significant delay range (<70)
- Language skills decreased significantly with age, with an adjusted R2 of 0.201 (P=0.031). Excluding the biochemical variant patient, adjusted R2 = 0.344 (P=0.006, Figure 1).

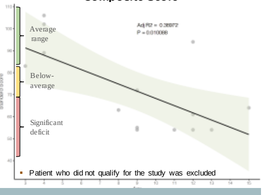
Figure 1 – Oral and Written Language Scales: Oral Expression



Cognition

- Cognition was assessed in 14 of 19 children.
  - **Younger age group** (2–6): the majority of patients (3/4; 75.0%) had a standard score in the average range (86–115); 1 patient (25.0%) had a below-average standard score (71–85), and no patient had a score in the significant delay range (≤70)
  - **Intermediate age group** (7–12): the majority of patients (6/8; 75.0%) had a score in the significant delay range. 1 (12.5%) had a below-average standard score, and 1 (12.5%) was in the average range
  - **Older age group** (13–15) both patients (2/2; 100%) had a score in the significant delay range
- Age-related decreases in cognition were significant, with an adjusted R2 of 0.390 (P=0.010; Figure 2).

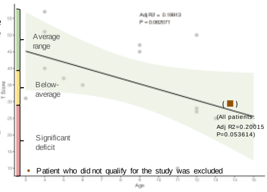
Figure 2 – NIH Toolbox Cognition Composite Score



Balance

- Balance was assessed in 17 of 19 children. Only 15 out of 19 children had a fully corrected T-score.
  - **Younger age group** (2–6): the majority of patients (4/6; 66.7%) had a standard score in the below-average range (31–40); 2 patients (33.3%) had average T-score (41–60), and no patient had a score in the significant delay range (≤30)
  - **Intermediate age group** (7–12): half of patients (3/6) had a score in the significant delay range and half (3/6) had average score
  - **Older age group** (13–15) 2 patients (2/3; 66.7%) had a score in the significant delay range, and 1 patient (1/3, 33.3%) had below average T-score
- Balance decreased across the age range, with an adjusted R^2 of 0.200 (P=0.054); Excluding the biochemical variant patient, adjusted R^2 = 0.199 (P=0.062; Figure 3).

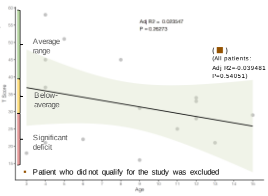
Figure 3 – NIH Toolbox Standing Balance Test



Dexterity

- 19 children completed the baseline dexterity assessment, only 17 had a fully corrected T-score.
  - **Younger age group** (2–6): 1 patient (1/7; 14.3%) had a T-score in the below-average range (31–40); 3 patients (3/7; 42.9%) had average score (41–60), and 3 patients (3/7; 42.9%) had a score in the significant delay range (≤30)
  - **Intermediate age group** (7–12): 3 patients (3/7; 42.9%) had a score in the significant delay range and 3 out of 7 were below average score. 1 patient had average score
  - **Older age group** (13–15) 2 patients (2/3; 66.7%) had a score in the significant delay range, and 1 patient (1/3, 33.3%) had average score
- Dexterity trended toward worsening, with an adjusted R2 of 0.039 (P=0.541); Excluding the biochemical variant patient, adjusted R2 = 0.024 (P=0.263; Figure 4)

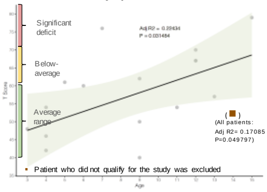
Figure 4 – NIH Toolbox 9-Hole Pegboard Dexterity Test



Behavior

- Caregivers of 18 children completed the BASC-3. For the Behavior Symptoms Index, higher scores indicate more risk.
  - **Younger age group** (2–6): the majority of patients (4/6; 66.7%) had a standard score in the average range (<60); 2 patients (2/6; 33.3%) were at risk (60–69), and no patient had a score in the clinically significant range (≥70)
  - **Intermediate age group** (7–12): 2 patients (2/9; 22.2%) had a score in the clinically significant range. 3 out of 9 (33.3%) were at risk, and 4 (4/9; 44.4%) were in the average range
  - **Older age group** (13–15) 1 patient (33.3%) had a score in the significant risk range and 2 out of 3 (66.7%) were in the average range
- Significant worsening of behavior (indicated by an increasing score in this test) was seen across the age range with an adjusted R2 of 0.171 (P=0.050). Excluding the biochemical variant patient, adjusted R2 = 0.224 (P=0.031; Figure 5).

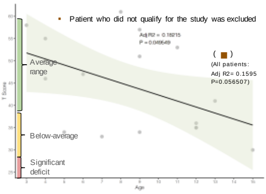
Figure 5 – BASC-3 Behavior Symptoms Index



Adaptive Skills

- Adaptive skills were also assessed with the BASC-3 in 18 children.
  - **Younger age group** (2–6): the majority of patients (5/6; 83.3%) had a standard score in the average range (41–60); 1 patient was in the at-risk range (31–40), and no patient had a score in the clinically significant range (≤30)
  - **Intermediate age group** (7–12): 4 patients (4/9; 44.4%) were at average, 5 patients (5/9; 55.6%) were at risk, and no one had a score in the clinically significant range
  - **Older age group** (13–15) 1 patient (33.3%) had a score in the significant risk range and 2 out of 3 (66.7%) were in the average range
- Age-related worsening in adaptive skills was observed. Including the biochemical variant patient, the endpoint were not quite statistically significant, with an adjusted R2 of 0.160 (P=0.057). However, excluding the biochemical variant patient, the endpoint reached significance with adjusted R2 = 0.182 (P=0.050; Figure 6).

Figure 6 – BASC-3 Adaptive Skills



Conclusion

- The study demonstrated statistically significant age-dependent worsening in language skills, cognition, behavioral symptoms, and adaptive skills in children with Classic Galactosemia. For motor function, i.e. balance and dexterity, there is a trend towards worsening with age; however, this observation did not reach statistical significance.
- While patients in the youngest age bracket were within the normal range or were moderately impaired on functional outcomes vs non-Galactosemia standard reference peer controls, older children and adolescents were severely impaired vs standard reference peer controls.
- This analysis confirms that Galactosemia is a slowly progressive neurological disease, and CNS function worsens over time despite strict adherence to a galactose-restricted diet. A need exists for intervention beyond dietary restriction to improve or prevent functional decline.
- The severity of CNS impact and significant decline in CNS outcomes with age underscores the importance of early intervention with a potential disease-modifying therapy in order to halt or prevent damage.

REFERENCES: 1. Rubio-Gozalbo ME, Haskovic M, Bosch AM *et al.* The natural history of classic galactosemia: lessons from the GalNet registry. *Orphanet J Rare Dis.* 2019;14:86; 2. Pyhtila BM, Shaw KA, Neumann SE, Fridovich-Keil JL. Newborn screening for galactosemia in the United States: looking back, looking around, and looking ahead. *JIMD Reports.* 2015;15:79–93; 3. Rasmussen SA, Daenzer JMI, MacWilliams JA, *et al.* A galactose-1-phosphate uridylyltransferase-null rat model of classic galactosemia mimics relevant patient outcomes and reveals tissue-specific and longitudinal differences in galactose metabolism. *J Inherit Metab Dis.* 2020;43:518–284. Waisbren SE, Potter NL, Gordon CM, *et al.* The adult galactosemic phenotype. *J Inherit Metab Dis* 2012;35:279-86; 5. Carrow-Woolfolk E. Oral and Written Language Scales (OWLS-II). 2nd ed. Torrance, CA: Western Psychological Services. 2011; 6. Gershon RC, Wagster MV. NIH Toolbox for assessment of neurological behavior and function. Bethesda, MD: National Institutes of Health. 2017; 7. NIH Toolbox Cognition Battery Composite Scores Technical Manual. 2012. (Accessed March 18, 2021, at https://www.healthmeasures.net/images/nihtoolbox/Technical_Manuals/Cognition/Toolbox_Cognition_Battery_Composite_Scores_Technical_Manual.pdf); 8. NIH Toolbox Standing Balance Test Technical Manual. 2012. (Accessed March 18, 2021, at https://www.healthmeasures.net/images/nihtoolbox/Technical_Manuals/Sensation/Toolbox_Standing_Balance_Test_Technical_Manual.pdf); 9. NIH Toolbox 9 Hole Pegboard Dexterity Test Technical Manual. 2012. (Accessed March 18, 2021, at https://www.healthmeasures.net/images/nihtoolbox/Technical_Manuals/Motor/Toolbox_9-Hole_Pegboard_Dexterity_Test_Technical_Manual.pdf); 10. BASC-3 Scales, Composites and Indexes for the TRS, PRS and SRP. 2019. (Accessed March 18, 2021, at https://images.pearsonclinical.com/images/assets/basc-3/CLINA15775-29093-BASC3-WhitePaper-Hr-f_FINAL.pdf.)

DISCLOSURES: SW, FL, RP, and SS are employees and stakeholders of Applied Therapeutics Inc

International Congress Inborn Errors of Metabolism 2021 Meeting November 21-24 2021
(Data first presented at ACMG March 22-26, 2021)

APPLIED THERAPEUTICS