JIMD Reports
DOI 10.1007/8904_2014_370

RESEARCH REPORT

Developmental Outcomes of School-Age Children with Duarte Galactosemia: A Pilot Study

Mary Ellen Lynch · Nancy L. Potter · Claire D. Coles · Judith L. Fridovich-Keil

Received: 23 April 2014 / Revised: 26 August 2014 / Accepted: 24 September 2014 / Published online: 15 February 2015

Abstract Duarte galactosemia (DG) is a mild allelic variant of classic galactosemia that results from partial impairment of galactose-1P uridylyltransferase (GALT). Although infants with DG are detected by newborn screening in some US states at close to 1/4,000 live births, most are discharged from follow-up very early in life and there is no consensus on whether these children are at increased risk for any of the long-term developmental delays seen in classic galactosemia. There is also no consensus on whether infants with DG benefit from dietary restriction of galactose. Reflecting the current uncertainty, some states choose to identify infants with DG by newborn screening and others do not. As a first step toward characterizing the developmental outcomes of school-age children with DG, we conducted a pilot study, testing 10 children with DG and 5 unaffected siblings from the same group of families. All children tested were between 6 and 11 years old. We used standardized direct assessments and parent-response surveys to collect information regarding cognition, communication, socio-emotional, adaptive behavior, and physical development for each child. Despite the small sample size, our data demonstrated some notable differences between cases and controls in socio-emotional development, in delayed recall, and in auditory processing speed. These results confirm that direct assessment of school-age children with DG can detect subtle but potentially problematic developmental deficits, and underscore the need for a larger study which has sufficient power to evaluate these outcomes while controlling for potentially confounding factors.

Communicated by: Gerard T. Berry, MD

Competing interests: None declared

M.E. Lynch
Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30322, USA

N.L. Potter
Department of Speech and Hearing Sciences, Washington State University, Spokane, WA 99210, USA

C.D. Coles
Department of Psychiatry and Behavioral Sciences, and Department of Pediatrics, Emory University School of Medicine, Atlanta, GA 30322, USA

J.L. Fridovich-Keil (✉)
Department of Human Genetics, Emory University School of Medicine, Emory University, Atlanta, GA 30322, USA
e-mail: jfridov@emory.edu

Introduction

Duarte galactosemia (DG) affects an estimated 1/4,000 live births every year in the United States (USA) (Fernhoff 2010; Pyhtila et al. 2014); this is close to 10 times the number who are affected by classic galactosemia (CG). Unlike the potentially lethal CG, which results from profound loss of galactose-1-P uridylyltransferase (GALT), DG occurs in patients who are compound heterozygotes for one mild (D or D2) and one severe (G) allele of *GALT*. Infants with DG demonstrate about 25% normal GALT activity (reviewed in (Fridovich-Keil and Walter 2008)) and as a result have difficulty metabolizing galactose – a sugar abundant in milk. Like patients with CG, infants with DG accumulate abnormally high levels of galactose metabolites following exposure to breast milk or milk formula (Ficicioglu et al. 2010).

Most infants diagnosed with DG in the USA come to clinical attention because of an abnormal newborn screening (NBS) result for galactosemia (Pyhtila et al. 2014). Median detection rates for DG vary widely among US states, from

essentially zero to more than 1/3,500 births; this range is believed to reflect differences in screening protocol rather than actual differences in prevalence (Pyhtila et al. 2014). Whether NBS *should* be used to identify DG infants, and whether DG infants benefit from early detection and dietary restriction of galactose in infancy, which is the practice in some states, remains unclear; doctors and public health professionals remain divided on the issue (Fernhoff 2010; Pyhtila et al. 2014).

The controversy surrounding DG stems largely from the reality that while the majority of children with classic galactosemia experience significant developmental deficits by the time they enter school (reviewed in (Fridovich-Keil and Walter 2008)), children with DG are generally discharged from follow-up as infants or toddlers so no one knows whether they are also at risk. Only two prior studies have addressed this question. One, by Ficicioglu and colleagues (Ficicioglu et al. 2008), involved direct testing of 28 toddlers and young children with DG, of whom 17 (mean age 3.5 years) consumed a lactose-restricted diet for their first year of life and 11 (mean age 2.2 years) consumed milk. Mean test scores for adaptive behavior, language, and cognitive development for both groups of children were within one standard deviation (1SD) of the reference mean, suggesting no significant deficits. However, these children were very young, and the study did not include a control group, making general conclusions difficult. The second study, by Powell and colleagues (Powell et al. 2009), involved a review of public health records to determine if children with DG were significantly overrepresented among students, 3–10 years old, receiving special educational services in the greater Atlanta metropolitan area. They were, with overrepresentation most pronounced among the older children. While provocative, this result suggesting that children with DG might be at increased risk of developmental deficits was indirect and potentially insensitive to milder developmental and educational effects.

As a first step toward assessing the specific developmental characteristics of school-age children with DG, we conducted a pilot study of 15 children ages 6–11 years – 10 with DG and 5 unaffected siblings recruited from the same group of families. Of the 10 children with DG, parents of seven had expressed concern regarding one or more developmental areas; parents of the other three said that they did not have concerns. Our goal was to assess how children with DG would perform relative to their unaffected peers in those areas of development known to be affected in children with CG (e.g., (Antshel et al. 2004; Bosch et al. 2004; Doyle et al. 2010; Potter et al. 2008; Potter et al. 2013)), using standardized tests of cognition, communication, socio-emotional, adaptive behavior, and physical development. In addition, we assessed how well a parent-response survey correlated with the results of direct testing.

Table 1 Demographic characteristics of study volunteers

Variable	Control group ($n = 5$)	DG: no parental concerns ($n = 3$)	DG: parental concerns ($n = 7$)
Child age in years, mean (SD)	7.56 (1.61)	7.26 (1.56)	9.79 (1.62)
Child gender (M:F)	1:4	1:2	3:4
Race[a,b]			
% Caucasian	80%	100%	85.7%
% Native American	20%	0	14.3%
Socioeconomic status rating[b] (Hollingshead score, mean (SD))	56.6 (5.4)	55.33 (9.24)	49.21 (9.37)
Sibs or parents with unexplained developmental, speech, or behavioral problems?	None	None	1 (yes, ADHD) 5 (no)[c]
Gross annual income[b]			
% <$100,000	20%	0%	71.4%
% ≥$100,000	80%	100%	28.6%

[a] Race was based on report of maternal background. All fathers were Caucasian

[b] For families in which two children participated (one DG and one unaffected sibling), the same parent/family information (race, income, SES) was included twice, once for each child

[c] Family history was unavailable for one child

Methods

Study Participants

Volunteers in the study included 10 children with DG and 5 unaffected siblings of children with DG, all 6–11 years old, who participated following informed consent and assent in Emory IRB protocol 00062977 (PI: ME Lynch). Demographic characteristics are presented in Table 1, and birth, diet, and diagnostic characteristics are presented in Table 2. Each child was accompanied by at least one parent. These families were recruited from among volunteers consented into a prior study of children identified by NBS as having DG (Emory IRB protocol 00024933 and GA PDH IRB protocol 130306, PI: JL Fridovich-Keil) who agreed to be recontacted and who lived within a two-hour drive of Atlanta. Of the 22 families in the recruitment pool, 14 (63.6%) responded with interest in participating, 12 were scheduled, and 11 actually participated. From parent survey responses collected in the earlier study, the 10 DG children in this study were categorized as having either no known parental concerns (3 children) or at least one developmental area of parental concern (7 children). Each child received a small prize for participating, but families were not reimbursed for travel and were not otherwise financially compensated.

Table 2 Birth and diet history, biochemical and *GALT* genotype data

Variable	DG: no parental concerns ($n = 3$)	DG: parental concerns ($n = 7$)
Birth weight and gestation	≥7 lbs, full term 6 lbs 15 oz, full term 5 lbs 10 oz (33 weeks twin)	≥7 lbs, full term (4) 6 lbs 13 oz, full term 6 lbs 10 oz, full term 4 lbs 15 oz (35 weeks, twin)
Traumatic birth or neonatal event?	None	None
Dietary galactose exposure in first year of life (soy: milk: other[a])	2:0:1	5:1:1
Available RBC GALT activity level[b] (μmol/h/g Hb)	8.9; 7.3; 7.1	8.2; 6.7; 6.1; 5.2; 4.8; 4.2; 3.3
Available *GALT* genotypes	Q188R/ N314D (2) 5 kb del/ N314D (1)	Q188R/ N314D (6) N314D/ unknown (1)
Available RBC Gal-1P (mg%) measured within 5 weeks of birth	25.1; 4.9; 0.5	15.9; 5.1; 2.1; 0.6; 0.2
Available urinary galactitol (mmol/mol creatinine) measured within 5 weeks of birth	154.6; 26.1	26.1; 27.4; <2.0

[a] Dietary galactose "other": In one case the infant drank soy until 6 months of age and then transitioned to milk; in the other case the child alternated feedings of breast milk and soy for the first year

[b] Reference range: The GALT enzyme activity reference range for unaffected controls is 22.2–45.8 μmol/h/g Hb, and for Duarte galactosemia, it is 2.5–9.5 μmol/h/g Hb

Procedures

All testing was conducted in a child development research laboratory of the Emory University Department of Psychiatry and Behavioral Sciences by psychologists and a speech-language pathologist/kinesiologist who were blinded to each child's case versus control status. Evaluations took about 2½ h per child, including breaks, and involved direct assessments of child cognitive ability, communication, auditory processing, and physical/motor development. Every child completed all of the assessments without apparent fatigue or concern. Parents were interviewed about family demographics and history as well as the child's general development, social skills, any problem behaviors, and participation, if any, in educational intervention or special education programs. Relevant biochemical and genetic lab results for study volunteers were obtained via a HIPAA waiver from the Emory Genetics Lab.

Outcome Measures

For this pilot study, we focused on developmental areas known to be affected in children with classic galactosemia (e.g., (Antshel et al. 2004; Bosch et al. 2004; Doyle et al. 2010; Potter et al. 2008; Potter et al. 2013)). Whenever a standardized measure was available, we used such an instrument to allow comparison with population norms in which standard scores (SS and *T*-scores) adjust for age and gender. The exceptions were the demographic and informational questionnaires developed for this pilot as well as the measurement of Auditory Brainstem Evoked Response (ABER), described below, and some of the measures of motor functioning. The measures used, with references, are listed in Tables 3 and 4.

To assess child socio-emotional development and behavior, we asked parents to complete interviews and rating scales concerning their child's behavior, general development, and social skills as well as to provide information about family background variables and any special education or educational intervention experiences their child may have had. Parent-response surveys included the Developmental Profile-3 (DP-3) (Alpern 2007), a developmental screening instrument; the Child Behavior Checklist (CBCL) (Achenbach and Rescorla 2001), which measures eight behavioral areas that can be problematic for school-age children; and the Social Skills Improvement System (SSIS) Rating Scales, Parent Form (Gresham and Elliott 2008), a measure of the child's social skills and problems, if any, with social interaction. Both the CBCL and the SSIS have scales that compare responses to those of children diagnosed with behavioral disorders, including autism and attention deficit hyperactivity disorder (ADHD). A number of aspects of cognitive development were assessed including global intelligence and visual-motor function, memory, working memory, processing speed, and sustained attention.

Auditory processing was measured with the ABER methodology using the Biopac STM100C stimulator (http://www.biopac.com/Manuals/app_pdf/app105b.pdf-ABER) as described previously (Kable et al. 2009; Salamy et al. 1975). This test is used in experimental contexts to measure aspects of auditory brainstem response such as latency to respond. Each ABER test was conducted in a quiet room with dim lighting by a trained tester who was blind to the case/control status of the child. Latency of the

Table 3 Measures used in direct child assessment

Variable	Measure
Cognitive skills	
Visual-motor skill	Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) (Beery et al. 2010)
Memory	Differential Abilities Scale, 2nd Edition (DAS-II) (Elliott 2007)
	Recall of Objects, Immediate and Delayed
Working memory	DAS II – Recall of Digits Forward, Recall of Digits Backward
Processing speed	DAS-II – Speed of Information Processing Test
Sustained attention	NEPSY – Visual Attention Task (Korkman et al. 1998)
Intelligence	Wechsler Abbreviated Scales of Intelligence-II (WASI-II) (Vocabulary and Matrix Reasoning subtests) (Wechsler 2011)
Language/communication	
Articulation	Goldman-Fristoe Test of Articulation-2 (Goldman and Fristoe 2000)
Receptive and Expressive language	OWLS-II Oral and Written Language Scales, Second Edition (Carrow-Woolfolk 2011) Listening Comprehension (LC) (receptive) and Oral Expression (OE) (expressive) subtests only
Auditory processing	Auditory Brainstem Evoked Response (see Kable et al 2009)
Movement/physical	
Balance, coordination, manual dexterity	Movement Assessment Battery for Children (MABC) (Henderson and Sugden 1992)
Tongue strength	Iowa Oral Performance Test (www.IOPImedical.com)

Table 4 Child behavior and social skills measures based on parent response

Variable	Measure
Social skills	Social Skills Improvement System (SSIS) Rating Scales (Gresham and Elliott 2008) Social Skills and Problem Behavior. Subscales (social skills): communication, responsibility, cooperation, assertion, empathy, self-control, engagement. Subscales (Problem Behavior): externalizing, bullying, hyperactivity/inattention, internalizing, autism spectrum
Behavior problems	Child Behavior Checklist (CBCL) 6–18 (Achenbach and Rescorla 2001). Provides scores on three broad dimensions of problem behavior (internalizing, externalizing, and total problems) and subscale scores (anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, aggressive behavior)
Developmental problems	Developmental Profile-3 (DP-3) (Alpern 2007). Provides screening information on possible developmental delay in five areas: physical, adaptive behavior, socio-emotional, cognitive, and communication
Participation in special education or intervention	Questionnaire developed by project staff to obtain information on parent concerns; school placement of child, services and interventions child experienced; medications for behavioral problems
Potential confounding variables	Demographic Questionnaire (includes socioeconomic status)

auditory brainstem response peak from stimulus onset was determined using AcqKnowledge software from Biopac (see Biopac #AS105).

Speech articulation was assessed with the Goldman-Fristoe Test of Articulation 2 (GFTA-2; (Goldman and Fristoe 2000)). Receptive and expressive language were assessed using the Listening Comprehension and Oral Expression subtests of the Oral and Written Language Scales, Second Edition (OWLS-II). Tongue strength was assessed using the Iowa Oral Performance Instrument (IOPI) with the standard tongue bulb (IOPI Northwest 2005; (Potter et al. 2013)).

Physical/motor development measures included assessment of movement (balance, dexterity, and coordination/ball skills) and occurrence of pronounced visible tremors. Balance, manual dexterity, and ball skills were assessed using the Movement Assessment Battery for Children (MABC) (Henderson and Sugden 1992). The MABC included a shape-drawing task, which required the child to restrict his/her drawing to between the inner and outer lines. Hand tremors were scored as present or absent by the examiner (a kinesiologist) who noted if the participant exhibited an obvious kinetic tremor and was unable to draw a smooth line while completing the MABC fine motor task.

A formal assessment of kinetic tremor was not included in the pilot study protocol.

Analyses of Data

Due to the small sample size of this pilot study, we present each outcome category in descriptive terms, providing means and standard deviations (SD) as well as the proportion of children affected in each of the defined groups (controls; DG, total; DG, no parental concerns; DG, parental concerns) (Table 5). The cutoff limits for each range (e.g., normal range, borderline range, clinical range) were defined by the scoring instructions for the test – generally as a function of standard deviations from the control mean. The ABER is not a clinical test so there are no established norms; we therefore used analysis of variance (ANOVA) to assess differences between groups. Sib-sib comparisons, where available, are described in the text. To examine correlations between the parent report variables and corresponding direct testing outcomes, we used Pearson product moment correlations.

Results

Results are reported for analyses comparing variables among volunteers classified as DG, no parental concerns; DG, parental concerns; DG, total; or unaffected sibling controls. Results showing notable differences between the groups that may warrant further investigation are presented in Table 5.

Demographics and Family Information

Demographic characteristics of the study volunteers are presented in Table 1. There were no major differences in distribution of child gender, racial background, or socioeconomic status among groups; most families were European-American and of middle to upper-middle socioeconomic status. All mothers were currently married. All parents reported their children to be in good-to-excellent health at the time of the study. Child age was the only characteristic that differed notably among the groups, with children in the DG, parental concern group, being slightly older than the other groups. No child in the control group had a parent or sibling with unexplained developmental, speech, or behavioral problems. Among the DG volunteers, only one child, in the "parental concern" group, had a parent or sibling with unexplained developmental, speech, or behavioral difficulties (Table 1); family history information was unavailable for one child.

Birth and Diet History: Biochemical and *GALT* Genotype Data

In order to assess neonatal history and to better characterize the GALT deficiency and early galactose exposure for each DG child, we gathered birth and diet history information from the families and biochemical and *GALT* genotype data from the lab that performed the testing. As presented in Table 2, one child in each of the DG, no parental concern, and DG, parental concern groups, was a twin born early and at relatively low birth weight; all other children were born at term with normal birth weight. One child in the control group was also a twin born early and at low birth weight. None of the children in the study was known to have experienced a traumatic birth or neonatal event.

The majority of DG children in both the "parental concerns" and "no parental concerns" groups had experienced dietary restriction of galactose in infancy (Table 2); this was not surprising as this has been the intervention recommended for DG infants in Georgia. Biochemical lab results demonstrated a range of RBC GALT activities from 3.3 to 8.9 μmol/h/gHb and RBC galactose-1P and urinary galactitol levels in both groups ranging from normal to clearly elevated. The most elevated metabolite values were detected in one of the children in the DG, no parental concerns group.

Cognitive Outcomes

The cognitive cluster of direct assessments included measures of intelligence, visual-motor skill, memory, speed of information processing, and sustained attention. While intelligence was not affected, the pattern of results for the memory tests (Recall-Delayed and Recall of Digits Forward, a measure of auditory memory) suggested that DG children may have more difficulty in this area. For both these aspects of memory, children in the control group had higher scores than those in either the DG,no parental concerns, or the DG, parental concerns groups (Table 5). Other cognitive measures did not show notable differences in this small sample.

Auditory Processing (ABER)

Auditory processing was assessed as it is frequently associated with problems in language development and attention. When the pattern of means was examined for the auditory processing measure (Salamy et al. 1975), it showed longer latency on the initial wave for children in both the DG, no parental concerns, and the DG, parental concerns groups, than in the control group ($p < 0.04$, Table 5). Though our sample size was small, this finding suggests that children with DG may process auditory

Table 5 Notable preliminary findings from DG pilot study

Measure (construct measured)	Control group (mean ± SD) [$n = 5$]	Duarte galactosemia ($n = 10$)		
		DG combined (mean ± SD) [n = 10]	DG no parental concerns (mean ± SD) [n = 3]	DG parental concerns (mean ± SD) [$n = 7$]
Direct child assessments				
Digits forward[a] (*T*-scores) (memory) (normal range: borderline: clinical range)	58.4 ± 8.6 (5:0:0)	47.0 ± 7.8 (7:3:0)	50.0 ± 9.2 (2:1:0)	45.7 ± 7.5 (5:2:0)
Recall-delayed[a] (*T*-scores) (memory) (normal range: borderline: clinical range)	53.2 ± 4.0 (5:0:0)	49.0 ± 4. 8 (9:1:0)	43.6 ± 5.0 (2:1:0)	51.3 ± 2.4 (7:0:0)
ABER[b]: Latency Wave 1 (ms) (auditory processing)	1.45 ± 0.11	1.65 ± 0.14*	1.58 ± 0.04*	1.67 ± 0.15*
OWLS-II[c]: Listening comprehension (SS) (receptive language) (normal range: borderline: clinical range)	118.6 ± 9.8 (5:0:0)	111.7 ± 12.4 (10:0:0)	122.0 ± 4.6 (3:0:0)	107.3 ± 12.2 (7:0:0)
OWLS-II[c]: Oral expression (SS) (expressive language) (normal range: borderline: clinical range)	111.4 ± 10.5 (5:0:0)	108.2 ± 10.6 (9:1:0)	110.3 ± 4.2 (3:0:0)	107.3 ± 12.7 (6:1:0)
MABC[d]: Total (percentile scores) (motor) (normal range: borderline: clinical range)	48.0 ± 43.2 (3:0:2)	25.2 ± 36.7 (3:1:6)	50.0 ± 38.7 (2:1:0)	14.6 ± 32.9 (1:0:6)
Tremor[e]: (motor) # without:# with pronounced hand tremor	4:1	6:4	3:0	3:4
Parent-response measures				
DP-3[f]: Socio-emotional (SS) (socio-emotional) (normal range: borderline: clinical range)	101.6 ± 9.0 (5:0:0)	84.7 ± 14.9 (4:5:1)	93.7 ± 14.2 (2:1:0)	80.9 ± 14.4 (2:4:1)
CBCL[f]: Withdrawn/depressed (*T*-scores) (socio-emotional) (normal range: borderline: clinical range)	50.8 ± 1.1 (5:0:0)	57.4 ± 7.2 (9:1:0)	50.7 ± 1.2 (3:0:0)	60.3 ± 6.7 (6:1:0)
CBCL[g]: Social problems (*T*-scores) (socio-emotional) (normal range: borderline: clinical range)	52.8 ± 5.2 (5:0:0)	57.9 ± 7.5 (7:3:0)	50.7 ± 0.6 (3:0:0)	61.0 ± 6.8 (4:3:0)
CBCL[g]: Thought problems (*T*-scores) (socio-emotional) (normal range: borderline: clinical range)	51.8 ± 2.1 (5:0:0)	56.7 ± 5.0 (9:1:0)	52.0 ± 1.7 (3:0:0)	58.7 ± 4.6 (6:1:0)
CBCL[g]: Attention problems (*T*-scores) (socio-emotional) (normal range: borderline: clinical range)	54.0 ± 6.0 (5:0:0)	60.6 ± 10.1 (6:4:0)	50.7 ± 0.6 (3:0:0)	64.9 ± 9.0 (3: 4:0)
CBCL[g]: Internalizing (*T*-scores) (socio-emotional) (normal range: borderline: clinical range)	43.8 ± 9.7 (5:0:0)	56.3 ± 8.7 (7:0:3)	49.7 ± 8.5 (3: 0:0)	59.1 ± 7.5 (4:0:3)
CBCL[g] Total problems (*T*-scores) (normal range: borderline: clinical range)	45.2 ± 13.4 (4:1:0)	55.4 ± 10.4 (7:1:2)	44.3 ± 6.5 (3:0:0)	60.1 ± 7.8 (4:1:2)
SSIS[h]: Problem (SS) (social/behavior) (normal range: borderline: clinical range)	97.8 ± 17.9 (4:1:0)	105.8 ± 17.3 (6:4:0)	86.3 ± 3.5 (3:0:0)	114.1 ± 13.2 (3:4:0)
SSIS[h]: Hyperactivity/inattention (raw scores) (social/behavior) (normal range: concern)	4.2 ± 3.8 (4:1)	7.7 ± 5.2 (6:4)	2.3 ± 1.5 (3:0)	10.0 ± 4.4 (3:4)
SSIS[h]: Autism spectrum (raw scores) (social/behavior) (normal range: concern)	7.2 ± 6.3 (4:1)	11.6 ± 5.3 (7:3)	5.7 ± 2.5 (3:0)	14.1 ± 3.9 (4:3)
Educational intervention (# not receiving: # receiving educational intervention in one or more areas)	5:0	5:5	3:0	2:5
Prescription medication for behavioral issues (# not taking:# taking prescription medication for behavioral issues)	5:0	7:3	3:0	4:3

[a] Differential Ability Scales, 2nd Ed
[b] Auditory Brainstem Evoked Response
[c] OWLS-II Oral and Written Language Scales, Second Edition (standard scores, SS)
[d] Movement Assessment Battery for Children
[e] Child had observable hand tremor and was unable to draw a smooth line
[f] Developmental Profile, 3rd Ed
[g] Child Behavior Checklist
[h] Social Skills Improvement System Rating Scale; SS = standard scores
*ABER scores are not used clinically and do not have normative ranges established. Though the sample size was small, analysis of variance (ANOVA) for these ABER scores indicated that the DG and control groups were distinct ($p < 0.04$)

information more slowly and may have relative difficulties in perception of speech sounds.

Communication

All children were within normal limits on measures of expressive and receptive language applied in this pilot (standard scores (SS) of 85–134 on the OWLS-II). The pattern of means, however, suggested that children in the DG, parental concerns group, may have lower listening or receptive language skills than those in the other two groups (Table 5). Two children in the DG, parental concerns group, also demonstrated speech sound disorders in the pilot (both with SS of 81 on the GFTA-2); one of these children was later diagnosed clinically with speech delay requiring therapy. One DG child who did not demonstrate a speech sound disorder in the pilot (at age 11) had been diagnosed with speech issues early in life and received speech therapy starting at age 3. Another DG child who did not demonstrate a speech sound disorder in the pilot was later diagnosed clinically with an expressive language deficit. All other children in the pilot study had normal speech production as measured in the pilot. All the children had normal tongue strength (max pressures of 34–81 kPa).

Physical/Motor Development

We used the Movement Assessment Battery for Children (MABC) to assess physical/motor development. Six of the seven children in the DG, parental concerns group, and two of the five children in the control group had total scores at or below the 5th percentile of the reference range on the MABC, which is the most frequently used cutoff score for diagnosing a coordination disorder (Potter et al. 2013) (Table 5). All of the children in the DG, no parental concerns group, had scores above the 5th percentile on motor skills, though one scored just above the cutoff (at the 6th percentile). Of note, four of the seven children in the DG, parental concerns group, had a pronounced kinetic hand tremor observed while attempting to draw a smooth line for the MABC fine motor tasks. One child in the control group, a sister of a child with observable tremor in the DG, parental concerns group, also had pronounced kinetic hand tremor when drawing. All other children tested in the pilot study were able to complete the drawing task without difficulty and with no pronounced tremors observed.

Socio-emotional and Behavioral/Social Skills Outcomes

Results from three ratings of socio-emotional outcomes suggested that functioning in this area was strongly affected in the children with DG. On the Developmental Profile-3 (DP-3), a screening measure, parents reported lower scores on the overall socio-emotional measure for children in the DG: parental concerns group when compared to the other two groups (Table 5). This finding from the DP-3 screening measure was confirmed using the more comprehensive Child Behavior Checklist (Table 5). Children in the DG, parental concerns group, were reported to have more problems on internalizing and total problems as well as higher problem scores on some of the subscales (withdrawn/depressed, social problems, thought problems, and attention problems). Parent ratings of their children's social skills, quantified using the SSIS instrument, again showed a similar pattern, with children in the DG, parental concerns group, showing higher scores than the other two groups on the problem behavior scale as well as on the hyperactivity/inattention and autism spectrum subscales.

Educational and Intervention Status

Parent report of the child's educational history was one of the factors used to classify DG volunteers into either the "parental concerns" or "no parental concerns" groups, so it was not surprising that parents in the DG "parental concerns" group were far more likely to report that they had concerns about their child's school performance, that the child had received intervention in at least one of seven areas, or that the child was taking medications for behavioral issues (Table 5). Only one child (in the DG, parental concerns group) had repeated a grade and the same child was the only one with an Individualized Educational Plan (IEP). In total there were three children in the sample taking medication for behavioral issues; they were all from the DG, parental concerns group (Table 5).

Relationship Between Parent-Response Results (DP-3) and Direct Testing for Outcome Parameters

Correlational analyses were completed for the pilot data to examine relations between the DP-3 parent rating scales and corresponding child outcome variables from direct testing. In general, we found that direct test results assessing a given outcome, for example, cognition or language, correlated significantly with the DP-3 scale screening for a similar construct, in this case cognitive and communication skills (Table 6). As expected, cognitive and language measures also correlated with some of the other outcome domains screened by the DP-3, for example, adaptive behavior, as these outcomes are related. As expected, we did not see correlations between cognition or language test results and parent-reported measures of physical development, as these outcomes are unrelated.

Table 6 Comparison of results from the DP-3 parent-response survey and direct tests of child cognitive and language development

	Pearson correlations between DP-3 parent ratings and direct testing summary measures of cognitive and language outcomes ($n = 15$)	
DP-3 scales	WASI-II full-scale IQ (cognitive measure)	OWLS-II oral expression (language measure)
Communication	0.705** ($p = 0.003$)	0.648** ($p = 0.009$)
Adaptive	0.757** ($p = 0.001$)	0.551* ($p = 0.033$)
Socio-emotional	0.654** ($p = 0.008$)	0.461 ($p = 0.084$)
Cognitive	0.785** ($p = 0.001$)	0.673** ($p = 0.006$)
Physical	0.287 ($p = 0.299$)	0.439 ($p = 0.102$)
General development	0.736** ($p = 0.002$)	0.646** ($p = 0.009$)

To examine the relationship between DP-3 parent-response survey results and some of the direct measures used to test developmental outcomes of children in this pilot study, we completed Pearson product–moment correlations using SPSS. Correlations calculated between each pair of variables are presented together with the two-tailed p-value for that computation
*$p < 0.05$
**$p < 0.01$

Comparisons Among Siblings

Our study volunteers included four sets of siblings, with one member of each set an unaffected control and the other a child with DG (one with no parental concerns, three with parental concerns). Looking at outcome measures that showed the greatest differences between cases and controls (e.g., ABER, digits forward, DP-3 social/emotional), we examined the data to query whether DG, control sib-pairs, had scores that were more alike than unrelated pairs. To the accuracy afforded by our small data set, the answer was no.

Discussion

We undertook this pilot study to assess how school-age children with DG would perform relative to their unaffected peers in areas of development either previously implicated as problematic in this population (Powell et al. 2009) or known to be affected in children with classic galactosemia (e.g., (Antshel et al. 2004; Bosch et al. 2004; Doyle et al. 2010; Potter et al. 2008; Potter et al. 2013)). We used a combination of standardized direct tests and parent-report surveys to assess cognitive, communication, socio-emotional, adaptive behavior, and physical development of 10 children with DG and 5 unaffected siblings, all ages 6–11 years old.

While our sample size was small, limiting the ability to control for other factors that might affect outcomes, we noted several key findings. Most important, we identified a number of specific areas of development where there was evidence of a difference in performance related to DG status. Of note, sometimes these deficits were recognized by parents as evidenced by skewed distribution between the DG, parental concerns, and DG, no parental concerns groups; other times these deficits showed up in both DG groups.

The most pronounced areas of difference between cases and controls involved aspects of auditory processing, memory, and socio-emotional development. For example, children in both the DG, parental concerns, and DG, no parental concerns groups, demonstrated slower processing of auditory information (ABER) than children in the control group. This finding is of concern because slower auditory processing is frequently associated with problems in language development and attention. Consistent with this concern, two children in the DG, parental concerns group, demonstrated speech sound disorders in the pilot and three DG children from the study demonstrated speech or expressive language difficulties in clinical testing. Interestingly, a younger brother from one of the families whose DG child in the study was categorized as “no parental concerns” was later diagnosed clinically with apraxia of speech and learning delay. This child, who was too young to be included in the pilot, also has DG.

Children in both the DG, parental concerns, and the DG, no parental concerns groups, also showed evidence of less efficient auditory memory when assessed using Recall of Digits Forward, one of the memory tasks in the cognitive protocol. Children in the DG, parental concerns group, also showed evidence of lower listening or receptive language skills than children in the other two groups. These problems may be related only to auditory processing, but there may also be a contribution from memory. Further exploration of these functions in a larger sample will allow us to answer this question.

With regard to socio-emotional development, results of CBCL and SSIS ratings suggested that children in the DG, parental concerns group had greater internalizing problems (e.g., anxiety, depression) as well as difficulties with social behavior compared with controls. These problems were similar to those reported previously in individuals with classic galactosemia (Antshel et al. 2004; Bosch et al. 2004; Ryan et al. 2013; Waisbren et al. 2012). Parent reports on the SSIS Autism Spectrum subscale indicated that one of five control children and three of seven DG children in the study scored in the “concern” range. Specific symptoms of concern assessed in this section of the SSIS survey included heightened anxiety, social problems, and social withdrawal. As noted above, these same sorts of internalizing behaviors have also been reported for patients with

classic galactosemia (Antshel et al. 2004; Bosch et al. 2004; Ryan et al. 2013; Waisbren et al. 2012). Children in the DG, no parental concerns group did not exhibit these issues, which is not surprising considering that both the CBCL and SSIS are parent-response surveys, and earlier parent reports were used to stratify the DG children into "parental concern" and "no parental concern" groups.

While it is clearly possible that some of the developmental deficits we observed among our study volunteers with DG reflected ascertainment bias of the sample, the overlap between our results and those reported by Powell and colleagues (Powell et al. 2009), that were not subject to the same ascertainment bias, is concerning. That some of these deficits were found among children in both the DG, parental concerns, and DG, no parental concerns groups, also suggests that ascertainment bias cannot fully account for our observations.

Laboratory studies demonstrated that all of the children with DG had GALT activity, RBC Gal-1P, and urinary galactitol levels in the expected ranges for infants with Duarte galactosemia; in fact, the highest Gal-1P and urinary galactitol levels were reported for a child in the DG, no parental concerns group, suggesting that abnormal neonatal metabolites were not a deciding factor in determining long-term outcome. Finally, that almost all of the DG children included in our pilot study experienced dietary restriction of galactose in the first year of life raises the question of whether a population of DG children who consumed milk in infancy might have demonstrated similar or perhaps different outcomes.

Conclusion

The results of our pilot study support the hypothesis that DG patients, as a group, may experience subtle developmental deficits by mid-childhood that could impact child health and well-being, including deficits in auditory processing, memory, and socio-emotional development, among other areas. As this was a very small pilot study and confined in terms of socioeconomic status and other variables, it is not clear if these results will be generalizable to the DG population as a whole. In addition, since the sample was recruited from a state (Georgia) that generally recommends dietary restriction of galactose in the first year of life for newborns diagnosed with DG, interpretation of results cannot answer questions regarding the impact of such restrictions. The concerns raised by this pilot study underscore the need for a larger study to assess developmental outcomes of school-age children with DG who reflect the full spectrum of galactose exposure in infancy with a sample size sufficient to control for other familial and social factors that may affect outcomes. If our pilot results are confirmed in such a study, they may offer the possibility of early identification and either proactive or reactive intervention to improve the long-term outcomes of at-risk children.

Acknowledgments First and foremost, we want to thank the 11 wonderful families who participated in this pilot research study; without them none of this work would have been possible. We also thank the many researchers from the Department of Psychiatry and Behavioral Sciences at Emory University who volunteered their personal time and professional expertise, including Julie Kable PhD, Karen Howell, PhD, Molly Millians EdD, Shital Gaitonde PhD, Elles Taddeo EdD, and Jonathan Cook. We are also grateful to Kelly Shaw for her assistance gathering lab results data. Finally, we are thankful to Dr. Brad Therrell of the National Newborn Screening Information System (http://nnsis.uthscsa.edu) for his encouragement and support of this project and to the University of Texas Health Sciences Center for providing initial funding for this work (Award# 0000017221, PI: Fridovich-Keil).

1-Sentence Synopsis

Direct assessment revealed a number of subtle but concerning developmental deficits among a cohort of 10 school-age children with Duarte galactosemia.

Compliance with Ethical Guidelines

Conflict of Interest

Mary Ellen Lynch declares that she has no conflict of interest.

Nancy Potter declares that she has no conflict of interest.

Claire Coles declares that she has no conflict of interest.

Judith Fridovich-Keil declares that she has no conflict of interest.

Informed Consent

"All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5)."

All data from specific individuals reported here were collected following appropriate informed consent and with approval by the Emory University Institutional Review Board (IRB# 00024933, PI: Fridovich-Keil and IRB#00062977, PI: Lynch).

Animal Rights

”This article does not contain any studies with animal subjects performed by any of the authors.”

Contributions of Each Author

Mary Ellen Lynch coordinated the pilot study described in this manuscript including IRB requirements, recruitment, and scheduling; served a lead role in assembling and analyzing the data presented; and helped write and edit the manuscript.

Nancy Potter served a lead role in data gathering during the pilot study and also helped to write and edit the manuscript.

Claire Coles helped coordinate the pilot study, served a lead role in data analysis and interpretation, and helped write and edit the manuscript.

Judith Fridovich-Keil initiated the project, coordinated the efforts of the other authors, conducted parent interviews during the pilot, and wrote most of the manuscript.

References

Achenbach T, Rescorla L (2001) Manual for ASEBA school-age forms & profiles. University of Vermont, Research Center for Children, Youth, & Families, Burlington

Alpern G (2007) Developmental profile, 3rd edn. Western Psychological Services, Los Angeles

Antshel K, Epstein I, Waisbren S (2004) Cognitive strengths and weaknesses in children and adolescents homozygous for the galactosemia Q188R mutation: a descriptive study. Neuropsychology 18:658–664

Beery K, Buktenica N, Beery N (2010) The Beery-Buktenica developmental test of visual-motor integration, 6th edn. http://www.pearsonassessments.com

Bosch AM, Grootenhuis MA, Bakker HD, Heijmans HS, Wijburg FA, Last BF (2004) Living with classical galactosemia: health-related quality of life consequences. Pediatrics 113:e423–e428

Carrow-Woolfolk E (2011) Oral and written language scales, 2nd edn. Pearson Assessments, Minneapolis

Doyle C, Channon S, Orlowska D, Lee P (2010) The neuropsychological profile of galactosaemia. J Inherit Metab Dis 33:603–609

Elliott C (2007) Differential ability scales, 2nd edition (DAS-II). Pearson, San Antonio

Fernhoff PM (2010) Duarte galactosemia: how sweet is it? Clin Chem 56:1045–1046

Ficicioglu C, Thomas N, Yager C et al (2008) Duarte (DG) galactosemia: a pilot study of biochemical and neurodevelopmental assessment in children detected by newborn screening. Mol Genet Metab 95:206–212

Ficicioglu C, Hussa C, Gallagher PR, Thomas N, Yager C (2010) Monitoring of biochemical status in children with Duarte galactosemia: utility of galactose, galactitol, galactonate, and galactose 1-phosphate. Clin Chem 56:1177–1182

Fridovich-Keil JL, Walter JH (2008) Galactosemia. In Valle D, Beaudet A, Vogelstein B, Kinzler K, Antonarakis S, Ballabio A (eds) The online metabolic & molecular bases of inherited disease. McGraw Hill, http://www.ommbid.com/

Goldman R, Fristoe M (2000) Goldman-Fristoe test of articulation, 2nd edn. Pearson Assessments, Minneapolis

Gresham F, Elliott S (2008) SSIS (Social Skills Improvement System) Rating Scales Minneapolis, MN: NCS Pearson, Inc, http://www.pearsonassessments.com

Henderson S, Sugden D (1992) Movement assessment battery for children manual. The Psychological Corporation Ltd., London

Kable J, Coles C, Lynch M, Carroll J (2009) The impact of maternal smoking on fast auditory brain responses. Neurotoxicol Teratol 31:216–224

Korkman M, Kirk U, Kemp S (1998) NEPSY: a developmental neuropsychological assessment. Psychological Corporation, San Antonio

Potter N, Lazarus J, Johnson J, Steiner R, Shriberg L (2008) Correlates of language impairment in children with galactosaemia. J Inher Metab Dis 31:524–532

Potter N, Nievergelt Y, Shriberg L (2013) Motor and speech disorders in classic galactosemia. J Inher Metab Dis Reports 11:31–41

Powell KK, Van Naarden BK, Singh RH, Shapira SK, Olney RS, Yeargin-Allsopp M (2009) Long-term speech and language developmental issues among children with Duarte galactosemia. Genet Med 11:874–879

Pyhtila B, Shaw K, Neumann S, Fridovich-Keil J (2014) Newborn screening for galactosemia in the United States: looking back, looking around, and looking ahead. J Inher Metab Dis Reports, epub ahead of print

Ryan E, Lynch M, Taddeo E, Gleason T, Epstein M, Fridovich-Keil J (2013) Cryptic residual GALT activity is a potential modifier of scholastic outcome in school age children with classic galactosemia. J Inher Metab Dis 36:1049–1061

Salamy A, McKean C, Buda F (1975) Maturational changes in auditory transmission as reflected in human brain stem potentials. Brain Res 96:361–366

Waisbren S, Potter N, Gordon C et al (2012) The adult galactosemic phenotype. J Inherit Metab Dis 35:279–286