Developmental Outcomes in Duarte Galactosemia

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OBJECTIVES: For decades, infants with Duarte galactosemia (DG) have been identified by newborn screening (NBS), but whether they should be treated with dietary restrictions of galactose has remained unknown. To clarify, we conducted a study of dietary and developmental outcomes in 206 children with DG (case patients) and 144 controls, all of whom were 6 to 12 years old.

METHODS: We recruited case patients from states where they were identified by NBS; unaffected siblings served as controls. Diet in infancy was ascertained by retrospective parent surveys; developmental outcomes were assessed in 5 domains, yielding 73 outcome measures for each child. We divided subjects randomly into independent discovery (n = 87) and validation (n = 263) sets. We tested the discovery set to order the 73 outcome measures by ascending P values and tested the 10 outcomes with the lowest P values for possible association with DG in the validation set. We also tested these same 10 outcomes for possible association with milk exposure in infancy among case patients in the validation set.

RESULTS: None of the 73 outcomes tested in the discovery set revealed significant association with DG, and none of the 10 outcomes tested in the validation set revealed either significant association with DG or significant association with milk exposure among children with DG.

CONCLUSIONS: Through our results, we demonstrated that there were no significant differences in outcomes tested between case patients and controls or among case patients as a function of milk exposure in infancy. In this study, we provide a long-needed foundation of knowledge for health care providers, families, and NBS professionals seeking to make evidence-based decisions about DG.

WHAT’S KNOWN ON THIS SUBJECT: Before this study, it was unknown whether children with Duarte galactosemia (DG) were at an increased risk for long-term developmental complications and whether exposure to milk in infancy, including breast milk, might contribute to those outcomes.

WHAT THIS STUDY ADDS: In this large study, we found no evidence of increased risks for developmental complications among children with DG regardless of milk exposure in infancy. This result provides a long-needed foundation of knowledge enabling evidence-based decisions about DG.

Duarte galactosemia (DG) is an autosomal recessive condition that affects $\sim$1 in 4000 screened births in the United States, and results from partial impairment of galactose-1-phosphate uridylyltransferase (GALT).DG is allelic to the potentially lethal disorder classic galactosemia (CG) that results from profound GALT deficiency and affects $\sim$1 in 50 000 screened US births. Unlike CG, most infants with DG remain apparently healthy after exposure to milk, which contains high levels of galactose. However, these infants do accumulate many of the same galactose metabolites seen in CG, although to a lesser extent. Whether older children with DG are at an increased risk for any of the long-term developmental complications seen in CG has remained unclear because most are discharged from follow-up as infants or toddlers.

The paradox of apparent good health in infants with DG despite elevated galactose metabolites has led to a range of opinions and treatment practices in DG. Specifically, some health care providers have argued that, considering the long-term negative consequences of even treated CG, elevated galactose metabolites in DG are of sufficient concern to warrant at least transient dietary restrictions of galactose, which rapidly normalizes metabolite levels. Others have countered that if the infant is thriving, elevated galactose metabolites alone are an insufficient reason to intervene, especially if the mother wishes to breastfeed.

Adding to the uncertainty, researchers in 2 previous studies in which the question of developmental outcomes in DG was addressed reported seemingly contradictory results. In the first study, Ficicioglu et al tested 28 toddlers and young children with DG. No significant abnormalities were seen when comparing the developmental outcomes assessed for these children to population norms. In a second report, Powell et al addressed the developmental outcomes of older children with DG indirectly by comparing newborn screening (NBS) records with available school records of 3- to 10-year-olds in the greater Atlanta area who had received special educational services. Of the 59 children with DG in this group, 8.5% had been diagnosed with or received special services for a speech or language disorder compared with only 4.5% of children without DG. When the age range was restricted to exclude children <8 years old, these percentages rose to 15.2% for children with DG and 5.9% for children without DG. Although the cohort sizes were small, the differences were deemed concerning.

This ongoing uncertainty about long-term outcomes and the role of infant diets in DG has also led to a disparity of practice in NBS for galactosemia. Specifically, those programs that set their GALT activity threshold to detect newborns with DG as well as newborns with CG generally experience a higher false-positive rate, which can be greater than or equal to threefold the number of diagnosed DG cases and $>30$-fold the number of diagnosed CG cases. Because each false-positive represents a family who receives notice of an abnormal NBS result for galactosemia, these numbers represent a substantial human cost in terms of parental anxiety and interrupted breastfeeding while awaiting the results of follow-up testing. Repeated testing and appointments also put an increased burden on the local health care system.

To help fill the knowledge gap about long-term developmental outcomes in DG and the potential role of milk exposure in infancy as a modifier, we conducted a case-control observational study of 350 children aged 6 to 12 years (206 with DG and 144 controls). Retrospective diet surveys revealed that $\sim$40% of the children with DG had consumed substantial dairy in infancy; 60% had not. We performed comprehensive direct assessments of child development in 5 outcome domains, yielding 73 separate outcome scores for each child. Using a data analysis plan that divided the full cohort into independent discovery and validation sets, we tested whether any outcome parameters were associated with DG status in the discovery set and then tested those 10 outcomes with the smallest $P$ values for possible association with DG status in the validation set. We also tested whether exposure to milk in infancy was associated with any of these 10 outcomes among case patients in the validation set. We found no significant differences in any of these tests. In this study, we provide a first direct test of diet and outcomes in older children with DG, and the results offer a long-needed foundation of knowledge for health care providers, parents, and NBS professionals seeking to make evidence-based decisions about DG.

**METHODS**

**Recruitment of Study Volunteers**

Families were recruited for participation in this study through letters addressed and mailed by collaborating state NBS programs or metabolic clinics after appropriate institutional review board (IRB) review and approval (Emory IRB Protocol 00081271; principal investigator: J.L. Fridovich-Keil). Families who responded expressing interest were evaluated for eligibility, assigned unique study and family identification codes, consented, and asked to complete an online survey for each eligible child.
Gathering Information About Diet, Developmental Outcomes, and Potential Covariates

Part 1 of the study consisted of a survey completed by a parent or guardian for each child gathering information about demographic factors, health, family, and diet, including breast milk and other dairy exposures in infancy. After completion of part 1, children who were deemed eligible (see Supplemental Table 4 for inclusion and exclusion criteria) were then invited to participate in part 2 of the study, which consisted of an additional parent or guardian response survey about the child’s educational and medical history followed by ~4 hours of in-person child assessment conducted locally by appropriately credentialed testers from our study team, ensuring consistency across testing blocks. For the in-person testing, participants completed a set of tests and subtests covering the following 5 main areas (see Supplemental Table 5): physical measures, cognitive development, socioemotional development, speech and hearing including auditory processing, and motor skills. Parents and guardians were also asked to complete surveys about their child’s behavior and their own parental stress. The testing schedule was arranged to balance case patients and controls, the order of testing, and the age and sex of participants among testers; all testers were blinded to the case-control status of all participants. Before analysis, the data collected were scored, verified by cross-checking between testers, and cleaned to ensure data quality.

Statistical Analysis

We performed all statistical analyses with R version 3.4.0. First, we used descriptive statistics to summarize study participant demographics, comparing these between DG cases and controls. We used the 2-sample t test for continuous covariates (age and IQ), Pearson’s χ² test for nominal variables with expected cell counts ≥5 (household income, breast milk exposure, parental education level, sex, and region of residence), and Fisher’s exact test for nominal variables with expected cell counts <5 (race and ethnicity). For each outcome measure, we then compared the proportion of missing observations in the full study cohort between DG cases and controls using Fisher’s exact test; for no outcomes did missing data associate with case-control status.

Next, we randomly assigned ~25% of study participants to a discovery cohort and the remaining 75% to a validation cohort; all related individuals were assigned to the same cohort to ensure the independence of the 2 sets. We compared demographic characteristics between discovery and validation set members using the tests described above; the sets were well balanced for all characteristics (Table 1).

For each of the 73 outcome measures collected on study participants (see Supplemental Table 6), we first identified the relevant covariates that required adjustment using stepwise variable selection with the Bayesian information criterion in the full study cohort. In the discovery set, we then fit a mixed-effect regression model (linear, logistic, or ordinal) for each outcome measure that included DG status and selected covariates as predictor variables. Because controls were the unaffected siblings of case patients, this mixed model incorporated family-level random intercepts and therefore took into account within-family correlations of observed outcome scores. For continuous outcomes, we also fit additional models in which the outcome measures were first log transformed, square root transformed, or rank transformed to normality. We compared diagnostic residual plots of these models to determine if transformation yielded considerable improvement in model fit over the untransformed data for a given outcome. We performed likelihood ratio tests for the significance of the DG term in each model and ranked outcomes by the resulting P values.

Finally, we selected the 10 outcome measures with the smallest P values from the discovery set analysis and fit the corresponding models in the validation set. We then filtered the validation set to include only DG subjects and, for each of the 10 selected outcome measures, fit a model that included milk exposure and relevant demographic covariates as predictor variables. We performed likelihood ratio tests to identify which outcomes, if any, revealed (1) significant association with DG status in the validation set and/or (2) significant association with milk exposure among case patients with DG in the validation set. Given that 20 total hypotheses were tested in the validation set, we used a Bonferroni-adjusted P value threshold for a significance of α = .05/20 = .0025.

RESULTS

Study Participants

Case patients were children with DG, aged 6 to 12 years, recruited from 17 US states plus the District of Columbia with the assistance of local NBS programs or metabolic clinic colleagues who mailed IRB-approved recruitment envelopes to eligible families from their records. Controls were unaffected siblings, also 6 to 12 years old, recruited from these same families. All study participants were consented in accordance with Emory University and local IRB policy, and case-control status was confirmed by full \textit{GALT} gene sequencing of DNA from saliva samples. In Table 1, we present demographic and other relevant characteristics of study participants as subdivided into independent discovery and validation.
sets. Case and control cohorts were well matched on all parameters except exposure to breast milk, which was substantially higher for controls (Table 1). This difference is consistent with the dietary recommendation given to many families to restrict milk in favor of nondairy formula for infants with DG. In Supplemental Table 7, we present the distribution of GALT genotypes of children classified in this study as case patients and controls or of those excluded from the study.

Do Children With DG Show a Higher Prevalence of Developmental Complications?

All children were assessed for developmental outcomes representing the following 5 general domains: physical measures, cognitive development, motor development, speech and hearing, and socioemotional development (Supplemental Table 4), as described in our Methods section. These domains yielded a total of 73 unique outcome scores for each child (Supplemental Table 5).

To maximize the statistical power of our study while minimizing bias in selecting the outcomes to test, we split the 350 participant records randomly into independent discovery and validation sets to be tested sequentially, as described in our Methods section. These sets were well matched for all covariates (Table 1). We tested the discovery set (n = 87) for possible association of DG status with each of the 73 outcomes, ordering the outcomes by increasing raw P values. If all null hypotheses were true (ie, no outcomes were, in truth, significantly associated with DG status), by chance we would still expect 3.65 of the 73 outcomes to reveal nominal significance (raw P < .05); we saw 4. Next, we tested the 10 outcomes revealing the smallest P values even close to this threshold (Table 2). In Fig 1, we show box and whisker plots of case and control outcome scores from both the discovery and validation data sets for each of the 10 outcomes listed in Table 2.

### TABLE 1: Demographic Characteristics of Participants in This Study

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Discovery Set</th>
<th>Validation Set</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, mean ± SD</strong></td>
<td>9.4 ± 1.7</td>
<td>9.3 ± 2.2</td>
</tr>
<tr>
<td><strong>Annual household income, n (%)</strong></td>
<td>10 (30.3)</td>
<td>9 (18.0)</td>
</tr>
<tr>
<td><strong>Less than average for state</strong></td>
<td>19 (22.9)</td>
<td>17 (16.2)</td>
</tr>
<tr>
<td><strong>Average for state</strong></td>
<td>22 (26.9)</td>
<td>29 (29.8)</td>
</tr>
<tr>
<td><strong>Greater than average for state</strong></td>
<td>28 (31.6)</td>
<td>51 (51.7)</td>
</tr>
<tr>
<td><strong>Breast milk exposure, n (%)</strong></td>
<td>31 (62.0)</td>
<td>66 (62.9)</td>
</tr>
<tr>
<td><strong>Highest parental education, n (%)</strong></td>
<td>53 (63.9)</td>
<td>97 (63.0)</td>
</tr>
<tr>
<td><strong>Race and ethnicity, n (%)</strong></td>
<td>65 (75.4)</td>
<td>163 (62.9)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td>54 (62.1)</td>
<td>85 (53.2)</td>
</tr>
<tr>
<td><strong>US region of residence, n (%)</strong></td>
<td>54 (62.1)</td>
<td>139 (52.5)</td>
</tr>
</tbody>
</table>

GED, General Educational Development.
TABLE 2 Top 10 Outcomes From the Discovery Set Also Tested in the Validation Set for Possible Association With DG

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Covariates</th>
<th>Discovery Set P Value</th>
<th>Validation Set P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ABER wave 3 latency</td>
<td>Age, sex, and region</td>
<td>.024</td>
<td>.513</td>
</tr>
<tr>
<td>2. NG mean error spiral 1 for right hand</td>
<td>Age and sex</td>
<td>.034</td>
<td>.135</td>
</tr>
<tr>
<td>3. NG completion time spiral 1 for left hand</td>
<td>—</td>
<td>.041</td>
<td>.126</td>
</tr>
<tr>
<td>4. WISC IV integrated spatial span backward standard scaled score</td>
<td>Region</td>
<td>.049</td>
<td>.919</td>
</tr>
<tr>
<td>5. NG RMSE spiral 1 for right hand</td>
<td>Age and sex</td>
<td>.056</td>
<td>.224</td>
</tr>
<tr>
<td>6. ABER wave 5 latency</td>
<td>Age, sex, and region</td>
<td>.060</td>
<td>.677</td>
</tr>
<tr>
<td>7. NEPSY II route finding score percentile</td>
<td>Sex and IQ</td>
<td>.066</td>
<td>.038</td>
</tr>
<tr>
<td>8. NEPSY II word generation initial letter scaled score</td>
<td>IQ</td>
<td>.069</td>
<td>.779</td>
</tr>
<tr>
<td>9. Head circumference</td>
<td>Age, breast milk exposure, race and ethnicity, sex, and IQ</td>
<td>.071</td>
<td>.045</td>
</tr>
<tr>
<td>10. BMI</td>
<td>Age, breast milk exposure, race and ethnicity, and region</td>
<td>.082</td>
<td>.173</td>
</tr>
</tbody>
</table>

Unadjusted P values are presented for the DG status regression coefficient. ABER, auditory brain evoked response; NG, neuroglyphics; RMSE, root-mean-squared error; WISC IV, Wechsler Intelligence Scale for Children, Fourth Edition; —, not applicable.

FIGURE 1
Top 10 outcomes from the discovery cohort tested for possible association with DG status in the validation cohort. A, Box and whisker plots are presented for each continuous outcome revealing the distribution of scores for cases (DG) and controls from both the discovery and validation sets. Box outlines represent the 25th and 75th percentiles. Whiskers extend from upper and lower outlines to the most extreme data points within a distance of 1.5× interquartile range. B, Bar plots are presented revealing the distribution of ordinal scores for cases (DG) and controls from both the discovery and validation sets. ABER, auditory brain evoked response; NG, neuroglyphics; RMSE, root-mean-squared error; SS, scaled score.
Does Milk Exposure in Infancy Associate With Developmental Outcomes of Children With DG?

Finally, we tested each of the 10 outcomes listed in Table 2 for possible association with milk exposure in infancy among the 156 children with DG in our validation set. If all null hypotheses were true (ie, the distributions of all 10 outcomes were, in truth, identical between case patients who were milk exposed and those who were nonexposed), by chance this testing would be expected to yield 0.5 outcomes with nominal significance ($P < .05$); we saw 0. As above, the Bonferroni-adjusted cutoff for significance was $P = .0025$, and as no outcomes revealed even nominal significance, no outcomes revealed $P$ values close to this threshold (Table 3). In Fig 2, we show box and whisker plots of outcome scores for case patients who were milk exposed versus those who were unexposed from the validation set for each of the 10 outcomes tested.

**DISCUSSION**

In the study presented here, we ask the following 2 questions: (1) Do 6- to 12-year-old children with DG show an increased prevalence of developmental difficulties compared with controls? (2) Do 6- to 12-year-old children with DG who drank milk as infants show an increased prevalence of developmental difficulties compared with their counterparts who drank low-galactose formula? To the limits of our study, the answer to both questions was no. These results extend substantially from the pilot study by Ficicioglu et al, who found no developmental problems among a cohort of 28 toddlers and young children with DG. These results contradict the implications of Powell et al, who reported that 3- to 10-year-olds with DG were overrepresented among students receiving special educational services for speech and language in the greater Atlanta area. Potential explanations for the disparity include the limited size of the Powell et al cohort and the possibility that the difference in receipt of special services detected by Powell et al reflected a difference in access to services rather than a difference in the actual prevalence of speech and language difficulties. Of note, although we did not test ovarian function in this study, researchers in a previous study reported no significant difference in anti-Mullerian hormone or follicle-stimulating hormone levels between 57 girls with DG and 64 controls, effectively demonstrating that girls with DG, unlike their counterparts with CG, are not at high risk for premature ovarian insufficiency.

Of course, 1 formal interpretation of our results is that our study was simply underpowered to detect subtle developmental differences between case patients with DG and controls. However, a close review of the data signatures contradicts this hypothesis. For example, we did find some outcomes that differed nominally between DG cases and controls, but in all analyses the number of outcomes revealing raw $P < .05$ was comparable to the number of false-positives predicted by random chance under the null hypotheses. In addition, of the 4 outcomes that revealed nominally significant differences in the discovery set, none revealed even nominal significance in the validation set, and 3 revealed opposite directions of difference between case patients and controls in the discovery and validation sets. For the fourth outcome (Wechsler Intelligence Scale for Children spatial span backward), children with DG actually scored higher, not lower, than controls (Fig 1). Similarly, of the 2 outcomes that revealed nominally significant differences between cases and controls in the validation set (head circumferences and NEPSY-II: A Developmental Neuropsychological Assessment, Second Edition [NEPSY-II] route finding score, a submeasure of cognitive ability), neither revealed even nominal significance in the discovery set. For head circumference, the difference associated with DG status was far less than the difference associated with race, age, or sex, and for NEPSY-II route finding score, children with DG again scored higher, not lower, than controls.

Although the study described here is by far the largest and most comprehensive one reported to date for DG, it did have limitations. For example, even NBS programs

### TABLE 3 Top 10 Outcomes From the Discovery Set Tested in the Validation Set for Possible Association With Milk Exposure Among Case Patients With DG

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Covariates</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ABER wave 3 latency</td>
<td>Age, sex, and region</td>
<td>.810</td>
</tr>
<tr>
<td>2. NG mean error spiral 1 for right hand</td>
<td>Age and sex</td>
<td>.557</td>
</tr>
<tr>
<td>3. NG completion time spiral 1 for left hand</td>
<td>Region</td>
<td>.985</td>
</tr>
<tr>
<td>4. WISC IV integrated spatial span backward standard scaled score</td>
<td></td>
<td>.118</td>
</tr>
<tr>
<td>5. NG RMSE spiral 1 for right hand</td>
<td>Age and sex</td>
<td>.431</td>
</tr>
<tr>
<td>6. ABER wave 5 latency</td>
<td>Age, sex, and region</td>
<td>.253</td>
</tr>
<tr>
<td>7. NEPSY-II route finding score percentile</td>
<td>Sex and IQ</td>
<td>.814</td>
</tr>
<tr>
<td>8. NEPSY-II word generation initial letter scaled score</td>
<td>IQ</td>
<td>.606</td>
</tr>
<tr>
<td>9. Head circumference</td>
<td>Age, race and ethnicity, sex, and IQ</td>
<td>.807</td>
</tr>
<tr>
<td>10. BMI</td>
<td>Age, race and ethnicity, and region</td>
<td>.799</td>
</tr>
</tbody>
</table>

Unadjusted $P$ values are presented for the milk exposure regression coefficient in validation models. ABER, auditory brainstem evoked response; NG, neuroglycophils; RMSE, root-mean-squared error; WISC IV, Wechsler Intelligence Scale for Children, Fourth Edition; —, not applicable.
that identify infants with DG have some false-negatives; we observed this reality in our own cohort when reviewing GALT genotypes (some children initially enrolled as controls turned out to be case patients).

However, if those case patients with DG missed by NBS represent bias in our sample toward the more severely affected, the direction of the bias would actually tend to favor the conclusion of our study.

Other limitations include that although we tested a large number of developmental outcomes (73), there are outcomes we did not test, and so we cannot say if those might have revealed DG association.

FIGURE 2
Top 10 outcomes from the discovery cohort tested for possible association with milk exposure of DG infants in the validation cohort. A, Box and whisker plots are presented for each continuous outcome in case patients who were milk exposed (dairy) and those who were nonmilk exposed (no dairy). Box outlines represent the 25th and 75th percentiles. Whiskers extend from upper and lower outlines to the most extreme data points within a distance of 1.5x interquartile range. B, Bar plots are presented revealing the distribution of ordinal scores in case patients who were milk exposed (dairy) and those who were nonmilk exposed (no dairy). ABER, auditory brain evoked response; NG, XXX; RMSE, root-mean-squared error; SS, scaled score.
Our age range was also limited (6–12 years old); outcome differences seen only earlier or later would have been missed. In addition, parent-reported child dietary information was retrospective, and given that most families lived in states where diet recommendations for DG were mixed 6 to 12 years ago, we had no clear way to cross-check the information. Of note, some parents told us they chose what to feed their infant by doing their own research, often using social media and not always following a doctor’s recommendation. Also, all 350 study volunteers included in the final analysis were from 13 states in the continental United States, and as predicted by allele frequencies in different racial groups, the overwhelming majority of study participants were white. Whether the results might have been different with a different study cohort is unknown. Finally, although we were able to test and adjust as needed for numerous covariates, there were 2 we could not adjust for: birth order and breast milk exposure. Specifically, because we recruited families to the study on the basis of having at least 1 child with DG, our participant cohort included some case patients who were only children but no controls who were only children. In addition, when comparing between case patients who were milk-exposed and those who were nonexposed, by definition we could not adjust for breast milk exposure as a covariate.

CONCLUSIONS

The implications of our results are broad and important for families and health care providers of infants with DG choosing what to feed their infant. These results are also relevant for the families of older children with DG experiencing developmental complications; if the specific complication is not seen at a higher prevalence among children with DG, the family might want to look for other possible causes. Finally, our results are important for public health professionals deciding whether NBS for galactosemia should be designed to detect DG as well as CG. As documented previously, adjusting the NBS GALT activity cutoff to below the level seen for most infants with DG can dramatically lower not only the number of infants with DG identified but also the number of false-positives without compromising the detection of infants with CG. If infants with DG are not at an increased risk for developmental complications and do not benefit from dietary restrictions of galactose, it may be best to avoid subjecting them to the stress, potentially interrupted breastfeeding, and follow-up testing associated with receipt of an NBS-positive result for galactosemia.

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ABBREVIATIONS

CG: classic galactosemia
DG: Duarte galactosemia
GALT: galactose-1-phosphate uridylyltransferase
IRB: institutional review board
NBS: newborn screening
NEPSY-II: NEPSY-II: A Developmental Neuropsychological Assessment, Second Edition

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