Duarte Galactosemia: How Sweet Is It?

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The pathologic consequences of various inborn errors of metabolism in the conversion of dietary and endogenously produced galactose through the Leloir pathway have recently been reviewed (1, 2). In this issue of the Journal, Ficicioglu and colleagues (3) report that children (ages 1–6 years) who have Duarte galactosemia (DG),2 a variant form of galactosemia, and are on a standard diet have typical concentrations of red blood cell (RBC) galactose 1-phosphate but increased concentrations of other galactose metabolites. The increased concentrations of galactose metabolites in these patients correlated with their dietary intake of galactose but not with any observable developmental or clinical pathology at this young age.

Why is this observation important? For more than 30 years in the US and many industrialized countries, most newborns have been routinely screened within 48 h after birth for classic galactosemia, along with multiple other genetic disorders, with a filter paper card containing a sample of dried blood (4). The primary purpose of the screen has been to detect newborns with classic galactosemia before they rapidly become symptomatic (severe liver failure, coagulopathy, sepsis, and death). If a screening result is consistent with classic galactosemia, the newborn is immediately switched from either breast milk or a cow’s milk formula to a galactose-restricted formula. If the diagnosis of classic galactosemia is confirmed by enzymatic and/or molecular testing, the affected child must maintain a lifelong diet that is severely restricted in galactose. Classic galactosemia is caused by the near total absence of galactose-1-phosphate uridylyltransferase (GALT) activity and the resulting accumulation of markedly increased concentrations of galactose and its metabolites. Depending on the population screened, classic galactosemia is found in approximately 1 in every 30 000 to 60 000 newborns (1, 2).

There are, however, many milder or variant forms of GALT deficiency. One of the more common forms detected in newborn screening is DG, which is caused by the inheritance of 1 Duarte gene and 1 classic galactosemia gene. The Duarte variant consists of the substitution of Asp for Asn at residue 314 (p.Asn314Asp), which causes bioinstability of the GALT enzyme. This variant leaves the child with about 25% of the wild-type GALT activity (2). Infants with DG are found much more frequently during newborn screening than those with classic galactosemia. During the last 3 years in the state of Georgia, we screened approximately 405 000 newborns and detected 8 children with classic galactosemia, but we detected 83 children with DG. Infants with DG remain asymptomatic but can have mildly to moderately increased concentrations of galactose metabolites while ingesting lactose from either breast milk or a cow’s milk formula. Early studies found many healthy adults with DG who had never been restricted in their lactose intake (5, 6). Since the beginning of newborn screening for galactosemia, the metabolic and newborn-screening communities have been split over whether newborns with DG require any dietary restriction of lactose or whether galactose intake during the first 6–12 months of life should be limited. Because of this controversy, several newborn-screening programs do not recommend any restriction of dietary galactose, whereas others recommend full or partial restriction of dietary galactose for at least the first year of life. This situation has caused confusion and consternation for parents and metabolism specialists. For those newborn-screening programs that recommend initial limitation of dietary galactose, substantial numbers of parents and their DG newborns must be located and brought to a metabolism center to receive nutritional and genetic counseling about the distinction between classic galactosemia and DG. These programs usually recommend that children with DG limit their feeding with breast milk or cow’s milk formula and replace it with a soya-based or a galactose-free infant formula. This counseling is done at considerable investment of time and expense by the public health system and metabolism clinics. There is also the concern that despite family counseling, infants with DG are mistakenly labeled with “galactosemia” and subjected to many years of unnecessary galactose restriction and testing.

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2 Nonstandard abbreviations: DG, Duarte galactosemia; RBC, red blood cell; GALT, galactose-1-phosphate uridylyltransferase.

Received April 26, 2010; accepted April 27, 2010.

Previously published online at DOI: 10.1373/clinchem.2010.147371
Ficicioglu et al. (3) demonstrated that older children with DG on a regular diet had typical concentrations of RBC galactose 1-phosphate, the galactose metabolite that is most often used to monitor the metabolic status of patients with galactosemia. These children, however, had increased concentrations of other less commonly monitored galactose metabolites, such as RBC galactitol and galactonate. Although it is reassuring that these children had typical liver functions, development, and ophthalmologic examinations, the question that still can be raised is whether as these children age, they might go on to develop complications secondary to their prolonged cellular exposure to the other less commonly monitored galactose metabolites.

Can this important and rather expensive public health issue be resolved? Do infants and children with DG require any restriction of dietary galactose? If so, for how long, and how should they be monitored biochemically? An ideal approach would be a long-term study of DG infants who would be randomized into 2 cohorts immediately after diagnosis. One cohort would be restricted in dietary galactose for the first year of life, and the other would not. The children would then be followed for their growth, nutritional, developmental, and ophthalmologic status, along with regular monitoring of routine and specific galactose metabolites, as described by Ficicioglu et al. The realistic concerns about such a study, however, include the feasibility of conducting the study over a sufficiently long time, given that complications from untreated DG might not be seen until adulthood. Additionally, there would be many study and bioethical issues to resolve. Perhaps a more plausible approach would be to conduct an epidemiologic investigation to locate a substantial number of adults 20–40 years of age who had DG detected at birth but whose galactose intake had never been restricted. This group would be compared to an age- and sex-matched population of adults to demonstrate whether adults with DG have any increased incidence of the problems seen in classic galactosemia, such as learning or language disabilities, neurologic difficulties, ophthalmologic disease (such as cataracts), or ovarian dysfunction, compared with the group of unaffected adults. This endeavor would be difficult and have many limitations, but it would provide valuable information about whether treating infants with DG is necessary. Public financing for such an investigation could be justified by the already considerable costs of genetic and nutritional counseling and the biochemical-monitoring costs incurred for the current newborn screening and metabolic programs that recall patients and restrict the galactose intake of those infants with DG. Are these public health funds being well spent? The metabolic- and newborn-screening communities have been asking this question for more than 30 years. Isn’t it time to find an answer?

**Author Contributions:** All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

**Authors’ Disclosures of Potential Conflicts of Interest:** No authors declared any potential conflicts of interest.

**Role of Sponsor:** The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

**References**


