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Minireview

Galactosemia: When is it a newborn screening emergency?☆

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ABSTRACT

Classic galactosemia is an autosomal recessive disorder of carbohydrate metabolism, due to a severe deficiency of the enzyme, galactose-1-phosphate uridyltransferase (GALT), that catalyzes the conversion of galactose-1-phosphate and uridine diphosphate glucose (UDPglucose) to uridine diphosphate galactose (UDPgalactose) and glucose-1-phosphate. Upon consumption of lactose in the neonatal period, the affected infants develop a potentially lethal disease process with multiorgan involvement. Since the advent of newborn screening (NBS) for galactosemia, we rarely encounter such overwhelmingly ill newborns. After ascertainment that the positive NBS indicates the possibility of galactosemia due to GALT deficiency, the critical question for the physician is whether the infant has the classic or a variant form of GALT deficiency, as classic galactosemia is a medical emergency. However, there are over 230 GALT gene mutations that have been detected around the world. Yet, most positive NBS tests are due to the Duarte biochemical variant condition or a simple false positive. In order to make the correct decision as well as provide informative counseling to parents of infants with a positive NBS, I utilize a relatively simple classification scheme for GALT deficiency. There are three basic forms of GALT deficiency: 1) classic galactosemia; 2) clinical variant galactosemia; and 3) biochemical variant galactosemia. The classic genotype is typified by Q188R/Q188R, the clinical variant by S135L/S135L and the biochemical variant by N314D/Q188R. In classic galactosemia, the erythrocyte GALT enzyme activity is absent or markedly reduced, the blood galactose and erythrocyte galactose-1-phosphate levels are markedly elevated, and the patient is at risk to develop potentially lethal *E. coli* sepsis, as well as the long-term diet-independent complications of galactosemia. Patients with the clinical variant form require treatment but do not die from *E. coli* sepsis in the neonatal period. If the clinician suspects galactosemia, even if based on clinical findings alone, then the infant should be immediately placed on a lactose-restricted diet. The purpose of this review is to help the clinician make the correct therapeutic decision after an NBS test has returned positive for galactosemia.

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1. Introduction

Classic galactosemia is an autosomal recessive disorder of carbohydrate metabolism (OMIM ID: 230400; [1–3]), due to a severe deficiency of the enzyme, galactose-1-phosphate uridyltransferase (GALT, EC

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2.7.7.12), that catalyzes the conversion of galactose-1-phosphate and uridine diphosphate glucose (UDPglucose) to uridine diphosphate galactose (UDPgalactose) and glucose-1-phosphate (Fig. 1). Upon consumption of lactose in the neonatal period, the affected infants develop a potentially lethal disease process with multiorgan involvement. However, since the advent of newborn screening (NBS) for galactosemia, we rarely encounter such overwhelmingly ill newborns. The following case report illustrates the acute neonatal toxicity that may be seen in infants with severe GALT deficiency, marked elevation of galactose-1-phosphate in target tissues and severe hypergalactosemia due to lactose ingestion.

2. Case report

A full term male infant with a normal birth weight who had been fed a proprietary formula containing lactose since birth was noted to be lethargic with poor feeding and temperature instability on day 6 of life. Following presentation in a local hospital, a sepsis workup was performed and antibiotics were administered to the infant. The newborn screening (NBS) tests performed on a dried blood spot (DBS) obtained on day 2 of life were reported positive for galactosemia on day 8: the total blood galactose was greater than 9 mg% (>500 μmol/L). A urine reducing substances test was performed and was 4+. The lactose containing formula was stopped and a soy-based formula was begun. Nevertheless, the infant's clinical condition continued to deteriorate. By day 10, the physical examination revealed that the infant was very quiet but arousable. There was poor skin perfusion, occasional spontaneous deep hyperventilation, jaundice and hepatomegaly. Laboratory testing revealed hyperbilirubinemia, hyperchloremic metabolic acidosis, mild elevations of plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST), prolonged prothrombin time (PT) and partial thromboplastin time (PTT) despite parenteral vitamin K administration, hypofibrinogenemia, and thrombocytopenia. The erythrocyte GALT enzyme activity was assayed in a biochemical genetics laboratory and was absent. Galactose-related metabolites were markedly elevated: the erythrocyte galactose-1-phosphate level was 34 mg% (1307 μmol/L; normal <1.0 mg% or <38 μmol/L), plasma galactitol level was 407 μmol/L (normal <1.0 μmol/L), and urine galactitol level was 4754 μmol/mmol creatinine (normal 2–78 μmol/mmol creatinine for infants<one year of age). As the neurological examination revealed an encephalopathic infant, a brain magnetic resonance imaging/magnetic resonance spectroscopy (MRI/MRS) was performed. On T2-weighted images signal intensities were increased in white matter in a patchy distribution; the most prominent abnormalities were in periventricular white matter, middle cerebellar peduncles and around the dentate nuclei. Diffusion-weighted images were compatible with intracellular swelling or cytotoxic edema. The brain MRS revealed double-shaped peaks at 3.67 and 3.74 ppm in occipital gray matter and basal ganglia voxels compatible with galactitol accumulation in brain cells at an apparent concentration of 8 mmol/L [4]. The patient was treated with phototherapy and given fresh frozen plasma. The sepsis workup proved negative. Gradually, over the next few weeks the acute encephalopathy, as well as the jaundice, hepatomegaly and bleeding diathesis resolved. By one year of age, and on diet therapy, the infant showed normal growth and development and a repeat brain MRI/MRS revealed absence of brain edema and no detectable galactitol. However, long-term follow-up indicated delayed language acquisition, speech defect, cognitive impairment and learning problems.

This case greatly illustrates the medical emergency that is classic galactosemia. It also underscores some of the enigmatic features of certain but not all patients with classic galactosemia. First, this was an infant who developed systemic toxicity despite NBS and who began treatment on day 8. The majority of infants with classic galactosemia who have had NBS DBS obtained on day 2 and are treated by 7 days of age do not manifest this degree of systemic toxicity. This patient appeared to be septic but the cultures were negative. It is possible that an unidentified organism was responsible and susceptible to the antibiotics, but failed to grow in the culture medium. Alternatively, the white matter edema may have been solely responsible for the encephalopathy, and the metabolic liver disease responsible for the abnormalities in coagulation. We usually think of newborns with galactosemia who have gone without treatment for 2–3 weeks as those who are most ill. However, severe signs and critical illness may be seen in the first week of life. For example, severe hyperbilirubinemia may be seen in the first 48 h of life [5] and death from *E. coli* sepsis has been noted as early as day 3 of life. The clinical and laboratory findings that may be detected in infants with classic galactosemia receiving lactose-containing breast milk or formula are shown in Tables 1 and 2, respectively. Note that almost no affected infant will manifest these findings if placed on a lactose restricted diet at birth. The appropriate treatment for an infant with classic galactosemia is to 1) eliminate a lactose-containing formula and breast feeding, and begin a formula such as a soy-based formula that contains no lactose as soon as possible; 2) monitor for signs of sepsis; and 3) monitor for signs of coagulopathy (Table 3).

Unfortunately, as with the patient in the case report, long-term complications are the rule rather than the exception in classic galactosemia. As the outstanding survey of Waggoner et al. showed in 1990 [6], these apparent diet-independent long-term complications even occur in patients who were started on diet therapy from day 1 of life. A list of the chronic long-term complications in classic galactosemia is shown in Table 4.

3. When is it an NBS emergency for galactosemia?

Classic galactosemia in a newborn infant is a medical emergency. The infant must be evaluated by a physician immediately and dietary lactose intake eliminated. The question then is when does the positive NBS indicate a high risk of classic galactosemia? The simple answer is when the GALT enzyme activity is absent and the galactose and

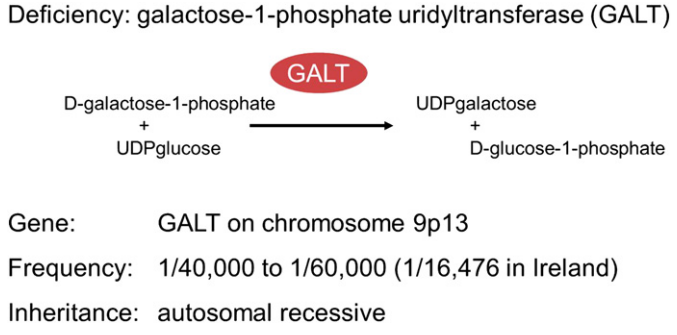

Fig. 1. Galactosemia.

Table 1
Clinical findings in galactosemic infants on lactose unrestricted diet.

Failure to thrive
Poor feeding
Vomiting
Diarrhea
Lethargy/coma[a]
Hypotonia
Bulging anterior fontanel[a]
Hepatomegaly[a]
Jaundice
Bleeding diathesis[a]
Sepsis[a]
Death[a]

[a] Uncommon in NBS era.

Table 2
Laboratory findings in galactosemic infants on lactose unrestricted diet.

Positive urinary reducing substances
Positive urinary protein
Increased serum indirect and/or direct bilirubin
Increased serum ALT, AST
Decreased serum fibrinogen
Prolonged PT, PTT[a]
Hypoglycemia[a]
Hyperchloremic metabolic acidosis[a]
Hypophosphatemia[a]
Generalized aminoaciduria[a]
Decreased hemoglobin/hematocrit[a]

[a] Uncommon in NBS era.

Table 3
Treatment of galactosemia in the newborn.

1) Eliminate lactose-containing formula and breastfeeding (use soy-based or elemental formula with no lactose).
2) Monitor for signs of sepsis.
3) Monitor for signs of coagulopathy (consider fresh frozen plasma).

Table 4
Long-term complications in GALT deficiency.

Speech defect	Hypergonadotropic hypogonadism or POI in females
Cognitive deficits	Reduced bone mineral density
Learning problems	Growth disturbance
Cataracts	Cerebellar ataxia/tremor/dystonia

galactose-1-phosphate levels are markedly elevated. However, the correct answer must reflect the practicalities of NBS in different locales. Not all public health laboratories utilize the same tests and the accuracy of some methods is better than others. For example, a laboratory may only measure total galactose or total and free galactose or GALT enzyme activity. A total galactose level includes both free galactose and galactose-1-phosphate. Laboratories vary in their total galactose cutoff ranging from 5 to 20 mg% (278–1111 μmol/L). Normal newborn infants ingesting lactose may have blood galactose levels as high as 8–10 mg% (444–556 μmol/L) and on occasion even a higher level but an erythrocyte galactose-1-phosphate level is normally less than 1 mg% (<38 μmol/L). However, unless the NBS laboratory provides an indirect estimate of galactose-1-phosphate by measuring both total and free galactose, only the total galactose may be reported giving a false impression of the possibility of galactosemia due to GALT deficiency. On day 2 of life, most infants with classic galactosemia ingesting "normal" amounts of lactose will have markedly elevated levels of both free galactose and galactose-1-phosphate. For example, in affected infants, the total galactose is likely to be greater than 20 mg% (1110 μmol/L) and the galactose-1-phosphate greater than 10 mg% (384 μmol/L). However, this is not always the case, as in the above infant. Some laboratories will measure total galactose first and if it is greater than their cutoff value, they will then measure GALT enzyme activity. If the activity is markedly reduced or absent, the infant will be considered to be at high risk for classic galactosemia. Given these uncertainties, my recommendation is that if the total galactose level is markedly elevated or the galactose-1-phosphate level is greater than 10 mg% (384 μmol/L) the infant be suspected of having classic galactosemia. This potentially life threatening disease should also be suspected if the GALT enzyme activity is absent regardless of the level of total galactose or galactose-1-phosphate. However, in all instances the clinical state of the newborn infant is key. If the clinician recognizes that the infant is ill, classic galactosemia should be suspected even if the total galactose level is not markedly elevated, or if the GALT enzyme activity is reduced but not absent. Under these circumstances the infant should be admitted to the hospital and lactose immediately eliminated from the diet. In these infants urine reducing substance tested while the infant is on a lactose-containing formula or being breastfed will be abnormal (at least 2+ and more likely 4+) if the infant has galactosemia.

4. Disorders of galactose metabolism

It is important to recognize that when a NBS program reports a positive result for galactosemia, not all infants will have classic galactosemia. If only the total galactose level is elevated, the first question is whether this is primary hypergalactosemia or secondary hypergalactosemia. Please see the ACMG ACT sheets and algorithms (http://www.acmg.net/AM/Template.cfm?Section=NBS_ACT_Sheets_and_Algorithms_Table&Template=/CM/HTMLDisplay.cfm&ContentID=5072, accessed 02/21/2012) for follow-up of NBS for galactosemia [7]. The primary hypergalactosemia disorders due to a defect in the galactose metabolic pathway of Leloir are shown in Fig. 2. They include 1) galactokinase (GALK, EC 2.7.1.6) deficiency (OMIM ID: 230200); 2) GALT deficiency; and 3) UDP-galactose-4′-epimerase (GALE, EC 5.1.3.2) deficiency (OMIM ID: 230350).

Galactokinase (GALK) deficiency is largely associated with cataracts although pseudotumor cerebri and other findings have been reported [1,3,8]. It is associated with an elevated blood galactose level and markedly reduced RBC GALK activity; the galactose-1-phosphate level is not elevated and GALT enzyme activity is not decreased (see Table 5). Long-term lactose restriction is warranted.

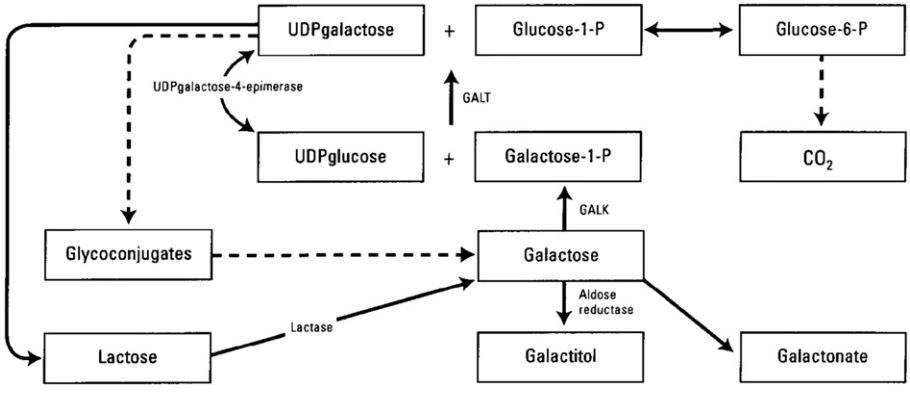

Fig. 2. Galactose metabolism.

Table 5
Primary hypergalactosemias.

Disease	Blood total galactose	Blood galactose	Erythrocyte galactose-1-phosphate	Urine galactitol
Galactokinase (GALK) deficiency	↑↑↑	↑↑↑	Normal or Low	↑↑↑
Galactose-1-phosphate uridyltransferase (GALT) deficiency	↑↑↑	↑↑	↑↑↑	↑↑
UDP-galactose-4′-epimerase (GALE) deficiency				
Benign ("peripheral")	↑	Normal	↑	Normal
Severe	↑	↑	↑	↑

Uridine diphosphate galactose-4′-epimerase (GALE) deficiency is usually not associated with clinical disease [1,3]. This type of GALE deficiency is termed the benign "peripheral" form of epimerase deficiency. While the erythrocyte enzyme activity is markedly reduced or absent, it is normal in tissues. It is associated with modestly elevated blood total galactose and galactose-1-phosphate levels; GALT activity is normal (Table 5). Several patients with reduced levels of GALE in cells other than RBC's such as lymphoblasts have been described [9]. Some have had developmental or growth delay or cataracts or even seizures, emesis and hypoglycemia in response to lactose ingestion but a cause and effect relationship between GALE deficiency and the clinical findings has not been established in each patient; the need for treatment remains unknown. However, there are at least five patients from two Pakistani families reported with systemic epimerase deficiency [10]. They have had severe neonatal-onset disease that resembles classic galactosemia. The generalized epimerase enzyme deficiency is both severe and widespread including deficiencies in liver and cultured skin fibroblasts. These patients need to be on a chronic lactose restricted diet. However, despite diet therapy, long term complications develop although the acute neonatal disease process does usually respond to dietary intervention. Some dietary galactose supplementation may be warranted to correct UDPgalactose deficiency in certain tissues such as liver [10].

There are several etiologies of secondary hypergalactosemia (see Table 6). They all center around liver dysfunction since the liver is the primary organ responsible for whole body galactose metabolism and disposal. When the liver is dysfunctional or damaged, lactose ingestion results in secondary hypergalactosemia. In addition, high levels of plasma galactose can result in elevated levels of erythrocyte galactose-1-phosphate even in the presence of normal erythrocyte GALT enzyme activity. Secondary hypergalactosemia may result in increased urinary excretion of galactitol. The causes include 1) congenital infectious hepatitis; 2) congenital hepatic arterio-venous malformations; 3) patent ductus venosus; 4) tyrosinemia, type 1, citrin deficiency (citrullinemia, type 2), and other metabolic disorders producing hepatocellular disease; and 5) Fanconi–Bickel syndrome due to GLUT2 deficiency. Thus, all infants with markedly elevated levels of blood galactose and/or galactose-1-phosphate on NBS need to be evaluated by the pediatrician for the presence of liver disease even if the enzyme activities of GALK, GALT and GALE are normal (please see the secondary ACT sheet and algorithm as noted above). I recommend that some infants with severe secondary hypergalactosemia be placed on a lactose restricted diet, even transiently, because of the risk of cataract formation.

Table 6
Secondary hypergalactosemia.

1) Congenital hepatitis
2) Congenital hepatic arterio-venous malformations
3) Patent ductus venosus
4) Tyrosinemia, type 1, citrin deficiency (citrullinemia, type 2), and other metabolic disorders producing hepatocellular disease
5) Fanconi–Bickel syndrome

5. Classification of the patient with GALT deficiency

After ascertainment that the positive NBS indicates the possibility of galactosemia due to GALT deficiency, the critical question then is whether the infant has the classic or a variant form of GALT deficiency. The Duarte variant form of galactosemia is far more frequent than the classic disease, since the c.-119_-116delGTCA + c. 940A > G (4 bp 5′ deletion + p.N314D) mutation, also known as Duarte D2, is so common in man [11]. However, there are other variant forms of GALT deficiency that are not benign and can be associated with significant clinical disease. An example is the clinically relevant variant S135L mutation, the most common allele in African Americans and native Africans in South Africa. Of great importance, there are over 230 GALT gene mutations that have been detected around the world [12-14]. The most common mutations are shown in Table 7.

In order to make therapeutic decisions and provide informative counseling to parents of infants with a positive NBS, I utilize a relatively simple classification scheme for GALT deficiency. There are three basic forms of GALT deficiency: 1) classic galactosemia; 2) clinical variant galactosemia; and 3) biochemical variant galactosemia. The classic genotype is typified by Q188R/Q188R, the clinical variant by S135L/S135L and the biochemical variant by N314D/Q188R. Please see Table 7 for a listing of several relevant genotypes that fall under each of the three categories. It is important to recognize that this classification of galactosemia is based not only on the biochemical phenotype but also on the potential for acute and chronic complications and the long-term prognosis. This becomes useful in counseling the parents of a new infant with a positive NBS test for galactosemia. For example, using the paradigm for classic galactosemia, the Q188R/Q188R genotype, it is clear that the majority of such patients are at risk for lethal *E. coli* sepsis, severe liver disease and cataracts in the neonatal period, and long-term complications including cognitive impairment, language delay, speech defects and, in women, premature ovarian insufficiency (POI) [15–21]. This is also true for the K285N/K285N, L195P/L195P and Ashkenazi Jewish Δ5.2 kb deletion/Δ5.2 kb deletion [15,22]. On the other hand, patients with the clinical variant type of galactosemia, exemplified by the S135L/S135L genotype [23-27], may manifest acute disease in the neonatal period including growth failure, liver disease and cataracts but usually fail to manifest the so-called diet-independent chronic complications of classic galactosemia including POI. In general, women with a S135L/S135L do not manifest POI and reduced fertility. It is possible that the first patient described in the American literature in 1935 by Mason and Turner [28] may have possessed a S135L allele. He was an African–American with clinical variant galactosemia and had a normal [^{14}C] galactose breath test [29]. African–Americans with variant disease and a normal [^{14}C] galactose breath test have no detectable GALT activity in erythrocytes, but approximately 10% residual activity in liver tissue [29-31]. This suggests but does not prove that patients with 10% or less residual GALT activity in liver require treatment with a lactose-restricted diet. As predicted, the African-American patient with a S135L/S135L genotype has a normal [^{13}C] galactose breath test [23,27,32]. Thus, we can use the [^{13}C] galactose breath test [33] to help define the biochemical phenotype in patients

Table 7
GALT genotypes and biochemical/clinical phenotypes.

Classic galactosemia	Clinical variant galactosemia	Biochemical variant galactosemia
Q188R/Q188R K285N/K285N L195P/L195P Δ5.2 kb del/Δ5.2 kb del	S135L/S135L[a]	4 bp 5′ del + N314D/Q188R[b]

[a] The original identification of the S135L mutation was exclusively in African–Americans but it is present on occasion in infants without known African–American heritage.
[b] Known as the very frequent "Duarte-classical galactosemia variant" or more often just the "Duarte variant."

with uncommon genotypes to help better characterize them as classic or clinical variant subjects. It is important to realize the most NBS public health laboratories do not distinguish between classic and clinical variant patients, and instead lump them together as classic galactosemia. From a treatment point of view, this is not unreasonable as both types of patients require treatment to prevent acute clinical disease, but from a counseling viewpoint, it is very undesirable as it may lead the physician to provide false information about complications to the new parents.

While there is controversy around the world regarding the correct management of the infant with the 4 bp 5′ deletion and N314D/Q188R Duarte genotype, it is generally accepted that infants, children and adolescents with this biochemical variant type of galactosemia do not manifest overt disease. I use the term biochemical variant as the patients usually show evidence of abnormal metabolite levels such as elevated erythrocyte galactose-1-phosphate in the first months of life and these may persist into late infancy and early childhood. While the term benign is often used to describe the Duarte D2 variant galactosemia state, there has never been a long term study of such individuals to demonstrate that the cognitive status, developmental parameters and the timing of hypothalamus–pituitary–ovarian axis landmarks are comparable to siblings with a normal GALT genotype [34]. On average, there is 25% residual erythrocyte GALT enzyme activity in the patient with a 4 bp 5′ deletion and N314D/Q188R Duarte genotype. But among various biochemical genetic laboratories, the residual activities range from 13% to 33%. Please note that the Duarte D1 or Los Angeles variant, L218L and N314D, does not cause galactosemia as each allele results in higher enzyme activity, i.e. greater than 115% activity [2].

In summary, this review of galactosemia and NBS provides a framework with which to approach the newborn infant with a positive screen for galactosemia. The key algorithmic points include the questions whether 1) is this a primary or secondary hypergalactosemia?; 2) is the primary hypergalactosemia due to GALK, GALT or GALE deficiency?; and 3) is this classic galactosemia due to severe GALT deficiency and, therefore, a medical emergency? If one is not sure, it is always better to err on the safe side, consider that the patient has a form of galactosemia that requires immediate therapy and stop all lactose intake.

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