Inborn Errors of Metabolism with Hepatopathy

Metabolism Defects of Galactose, Fructose, and Tyrosine

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KEYWORDS

• Galactosemia • Fructose intolerance • Tyrosinemia • Nitisinone • Liver • Liver disease • Inborn errors of metabolism • Hepatopathy

KEY POINTS

- If you think of galactosemia as a diagnostic possibility, eliminate the ingestion of lactose immediately.
- The elimination of sucrose, fructose, and sorbitol usually allows for normal growth and development in children with hereditary fructose intolerance.
- Diagnosis of tyrosinemia type I and the institution of nitisinone (NTBC) therapy are imperative to start early in the first year to eliminate the risk of hepatocellular carcinoma.

INTRODUCTION

As the largest internal organ of the body, the liver performs numerous vital functions and regulates many biochemical processes, including metabolism and the distribution of nutrients; interconversion of metabolites from ingested food; synthesis and secretion of biomolecules such as serum proteins, blood clotting factors, cholesterol, and bile acids; storage of glucose in glycogen form, as well as storing minerals and vitamins; and clearance of ammonia, bilirubin, toxins, and drug metabolites. Being in the center of the anabolic and catabolic pathways, the liver is affected by many inborn errors of metabolism. Common features of the hepatic pathophysiology involve inflammation, necrosis, cholestasis, and steatosis. Cholestasis can be seen in many metabolic disorders. Defects in bile acid metabolism, peroxisomal disorders, cholesterol biogenesis disorders, Neimann-Pick disease type C, and citrin deficiency

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(citrullinemia type 2) can present with cholestatic liver disease. Hepatocellular necrosis can result as a pathology of catabolic errors. The diseases of galactose, fructose, and tyrosine metabolism described in this article cause hepatocellular necrosis and liver failure. The manifestations of hepatocellular necrosis include jaundice caused by unconjugated hyperbilirubinemia, edema, ascites, hepatic synthetic failure, and hepatic encephalopathy. Elevated serum transaminases, hypoglycemia, hyperammonemia, hypofibrinogenemia, and hypoprothrombinemia can also be observed.[1] It should also be noted other inborn errors of metabolism may have liver involvement. For example, hepatomegaly or hepatosplenomegaly is observed in hepatic glycogen storage disorders, gluconeogenesis disorders, lysosomal disorders, and glucose transporter 2 deficiency (Fanconi-Bickel syndrome); Reye-like syndrome is associated with fatty acid oxidation and carnitine disorders. The diseases that may cause liver dysfunction are listed in **Boxes 1** and **2**.

GALACTOSEMIA OWING TO GALACTOSE-1-PHOSPHATE URIDYLTRANSFERASE DEFICIENCY

Key points

- Galactosemia is a medical emergency in the newborn period and ingestion of lactose should be eliminated immediately.
- Acute complications of the newborn period are resolved with dietary restriction of lactose.
- Despite dietary lactose and galactose restriction, long-term neurologic complications and primary ovarian insufficiency may be observed.

Clinical Description

Galactosemia is a metabolic disease associated with the failure of the interconversion of galactose to glucose (**Fig. 1**).[2] The first observation of classic galactosemia is described as "breastmilk induced neonatal nutritional toxicity" in 1908,[3] followed by a description of a similar infant with galactosuria in 1917.[4] Although the biochemical basis of the disease was still not identified, Mason and Turner[5] described the responsiveness of an infant with galactosuria and hypergalactosemia to a lactose-restricted diet. Two decades later, the enzyme defect was identified to be galactose-1-phosphate uridyltransferase (GALT) deficiency.[6] GALT is a critical enzyme in the Leloir pathway, the pathway responsible for the interconversion of galactose to glucose, and is responsible for the uridylation of galactose-1-phosphate so that it may undergo its final conversion to UDPglucose, performed by epimerase.

The pathology of GALT deficiency is directly related to the amount of residual GALT activity. Different common pathologic sequence variants in the *GALT* gene produce symptoms of galactosemia to varying degrees, which depend on the aspect of protein structure that they impair. As a result, galactosemia owing to GALT enzyme deficiency can be categorized into 3 groups based on residual enzyme activity: (1) classic galactosemia (0%–1% enzyme activity), (2) clinical variant galactosemia (1%–10% enzyme activity), and (3) biochemical variant (Duarte) galactosemia (15%–35% enzyme activity). In the clinical variant of galactosemia, the erythrocyte GALT activity may be around 1% to 10%, but certain genotypes (such as S135L/S135L) manifest absent or barely detectable enzyme activity in red blood cells; however, they have some enzyme activity (approximately 10% of controls) in the liver.[2] Classic galactosemia is very severe and Duarte galactosemia is often an incidental biochemical finding