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Review Article

Galactosemia a Disease that you Need to know

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Abstract

Galactosemia is an autosomal recessive disease, caused by the deficit of any of the four enzymes involved in the metabolism of galactose, derived from the disaccharide lactose, on its way to becoming glucose. Knowledge of this pathology and a high index of suspicion will allow early diagnosis and treatment, thus decreasing the associated complications and even mortality. We will present a brief summary of the disease in the context of a patient treated in our neonatology service.

Introduction

Galactose mainly comes from milk and its derivatives and is an important source of energy that must be converted to glucose to be used; galactosemia is an inborn error of the metabolism of galactose of autosomal recessive inheritance that generates significant morbidity that is potentially lethal. Four enzymes catalyze reactions to convert galactose into glucose in the Leloir pathway: the first enzyme, galactose mutarotase (GALM) catalyzes the reversible interconversion between β- and α-D-galactose, this is converted into galactose-1-phosphate (Gal-1-P) by galactose kinase (GALK); the next enzyme, galactose-1 phosphate uridyl transferase (GALT) converts Gal-1-P into glucose-1-phosphate (Glc-1-P) with the formation of UDP-galactose (UDP-Gal) of UDP-glucose (UDP-Glc) by a "ping-pong" mechanism. The latest enzyme galactose 4-epimerase (GALE) catalyzes the reversible conversion of UDP-Gal into UDP-Glc having as cofactor NAD^+. Galactosemia may be due to deficiency of any of the 4 enzymes [1]. In galactosemia, galactose accumulates in the cells and alternate metabolic pathways are activated causing the accumulation of toxic metabolites such as galactitol and galactonate that cause tissue damage [2]. The estimated overall frequency is 1 case per 62000 births [3], in the United States a prevalence of 1 case per 30000 to 60000 births has been reported [4], and in Italy in a population of 1123909 newborns screened a frequency of 1 case per 46830 births [5]. Galactosemia is one of the inborn errors of metabolism included in the panel of diseases that are screened, however, it is necessary to recognize the manifestations of the disease because in some countries there is no screening program for the disease; newborns with galactosemia caused by deficiency of galactose-1 phosphate uridil transferase (GALT) are normal at birth, within a few days of starting feeding they begin to have clinical manifestations of the involvement of various organs and systems, Table 1 shows the manifestations that an infant under 44 days of age presented at admission to our institution contrasted with those described in the literature; it had been an uncomplicated institutional term birth with discharge at 24 hours of age. He received breast milk, the result of neonatal TSH was 1.26 µIU / l, transfontanelar ultrasound and echocardiogram were performed and were normal, brain CT scan did not show microcalcifications, infection with toxoplasma, treponema pallidum, rubella, herpes I and II was ruled out. Polymerase chain reaction for cytomegalovirus showed 3381 copies, so he received hyperimmune immunoglobulin.

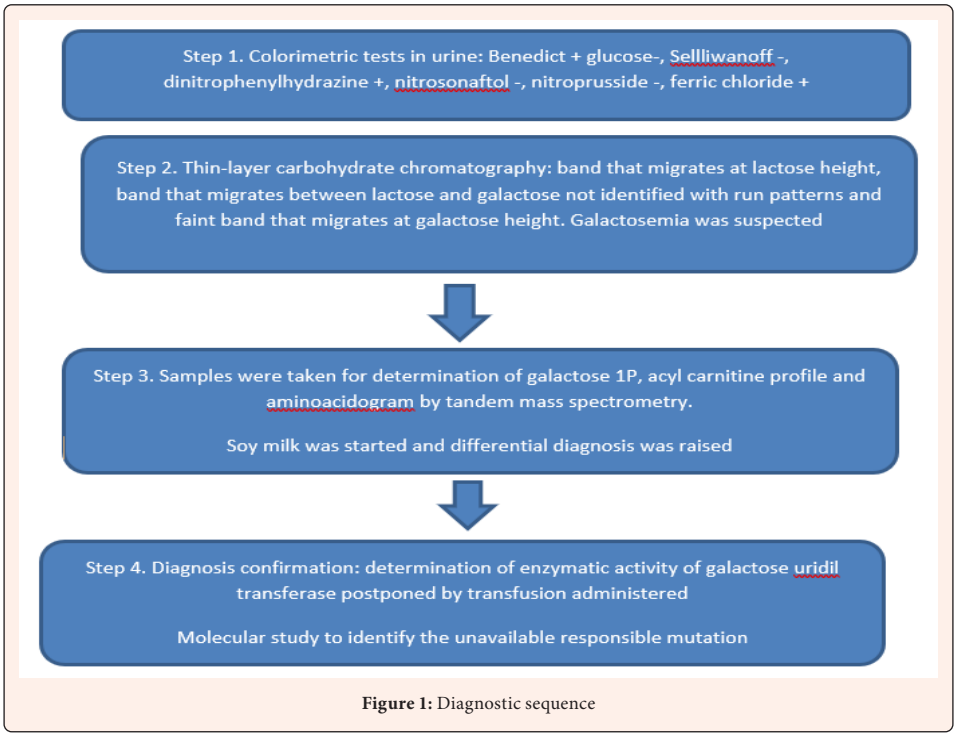

Figure 1: Diagnostic sequence

Table 1: Clinical manifestations of the minor infant contrasted with those described in the literature of classical galactosemia.

Described Disease Manifestations	References	Manifestations in the Infant
Food intolerance, growth failure	[6-9]	Dehydrated, hypotrophic Birth weight 3000 g On admission to the hospital: Weight 3800 g <°3 Height 56 cm <°50 Cephalic circumference 36 cm <°10
Vomit	[10]	
Hemolytic anemia, thrombocytopenia, neutropenia, gram-negative sepsis, Candida, recurrent sepsis (15-17), hemophagocytosis,	[7,8,10-12]	Hb 8.82 g Hto 26.02% VSG 40 mm/h, Reticulocytes 7.4% Negative urine culture.
Indirect hyperbilirubinemia with bilirubin encephalopathy and kernicterus.	[13]	
Decrease in chemotaxis and neutrophil bactericidal activity	[14]	
Purpura fulminans	[15]	
Jaundice, hepatomegaly, indirect hyperbilirubinemia to bilirubinic encephalopathy and subsequently cholestasis, hypoglycemia, increased aminotransferases, hypoalbuminemia, hypofibrinogenemia, prolongation of prothrombin and thromboplastin times Early liver failure	[5, 8-13,15,16]	Jaundice was the reason for remission, hepatomegaly, feces without acolia, ascites, collateral circulation. SGOT 522.5 U/L, SGPT 224.9 U/l, TB 18.43 mg%, DB 10 mg/dl, Alkaline phosphatase 407.2 U/L, Glycemia 32 mg%, Total proteins 5 g% Albumin 2 g%, PT 32,5´´ Control 11.3´´, INR 2.87, TPT 36.1´´, Control PTT 27.9´´ An abdominal ultrasound showed hepatosplenomegaly, grade II right and grade I left hydronephrosis. Free fluid in the abdominal cavity.
Hyperammonemia	[11]	
Tubulopathy, hyperchloremic metabolic acidosis, hypophosphatemia	[1,16]	Uroanalysis pH 6, density 1015, proteins 75, blood 250, bilirrubine +++, wbc 5-10x, Erythrocytes 2-4 x, granular cylinders + , BUN 6.4 mg%, creatinine 0.21 mg% Blood Gases pH 7,29, pCO2 28.7 pO2 29.2 HCO3 13.6 BE -12.9. Na 141.6 mEq/l, Cl 110.4 mEq/l, K 3.52 mEq/l Gap anion 17.6
Cataracts, vitreous hemorrhage	[7,9,11,17]	Bilateral cataracts.
Long QT syndrome	[10]	
Lethargy, hypotonia, chorea	[17,18]	Hypoactive, hyporeactive, irritable
Consanguinity	[15,17]	Parents are second-grade cousins
Reducing substances in urine + negative glucose, negative fructose	[8,9,15,16,18]	Benedict + glucose-, Sellliwanoff -
Chromatography determination of galactose	[15,16]	faint band that migrates to the height of galactose

With suspected metabolic disease as a cause of liver failure, colorimetric tests were ordered in urine, see step1, step 2, step 3 (Figure 1). During his stay he required transfusion of deleukocyte packed red blood cells; after the interventions the patient slowly evolved towards improvement, recovered from liver failure and the new ophthalmology evaluation showed almost complete resolution of cataracts, leaving the institution at 2 months of age. Quantification of Galactose-1-phosphate in blood by Tandem Mass Spectrometry: 0.57mmol/l (Reference value<0.50). The acylcarnitine profile and amino acid quantification were normal, which allowed to rule out tyrosinemia, citrine deficiency, organic acidurias and defects of beta fatty acid oxidation.

Discussion

The diagnosis of galactosemia does not seem difficult given the wide spectrum of clinical manifestations. The main one of them, jaundice, is a frequent manifestation in newborns since about 2/3 present it; however, it is a transient situation called habitual or physiological jaundice [19]. The jaundice that occurs in cases of galactosemia has special characteristics, it can begin as an unconjugated hyperbilirubinemia that can reach very high levels [13], or can become a cholestasis with high levels of conjugated bilirubin, so with the presentation of jaundice in newborns, with indirect bilirubin pattern or with cholestasis pattern, galactosemia should be included within the possible etiologies [1,13,18]; in addition, there is alteration of liver function until early failure, sometimes with hyperammonemia [11]. The medical history (interrogation and physical examination) is essential to find difficulties in feeding, the presence of vomiting, failure to thrive, the finding of hepatomegaly and hypotonia; in the interrogation, the history of consanguinity between the parents or neonatal death without diagnosis is an important issue. Since it is a multisystem disease, the search for the involvement of organs and systems must be broad through laboratory tests, imaging and interconsultations to specialists, looking for tubular damage, cataracts, among other findings. We believe that the case we present shows the involvement of various organs and systems because it is a late diagnosis, although early liver failure due to the disease has been reported. Galactosemia is a life-threatening disease for itself or for other complications like sepsis, so in countries like ours that do not have screening program for galactosemia, it should be investigated for the presence of clinical signs and symptoms. When there is no screening program, it is useful to find the presence of reducing substances in the urine [8, 9, 15, 16, 18] being able to demonstrate galactose in carbohydrate chromatography [16, 18], with this finding galactose should be suspended from the diet; quantification of galactose and galactose 1P is required.

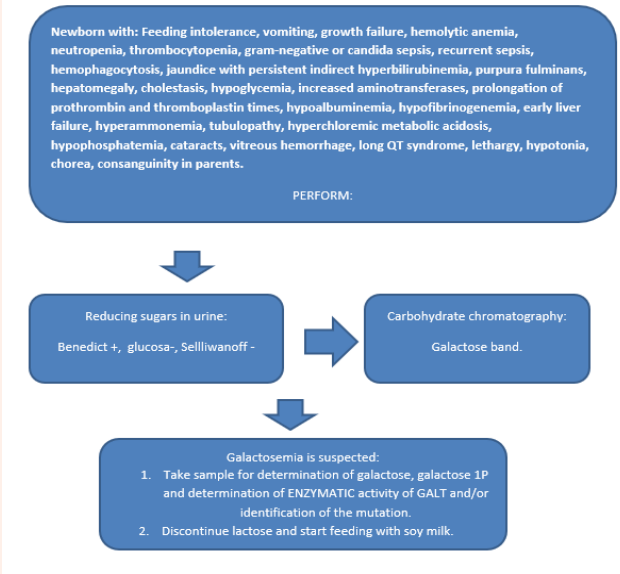

Figure 2: Diagnosis algorithm for galactosemia

The diagnosis is confirmed by demonstrating enzyme deficiency in erythrocytes or by molecular study to identify the responsible mutation. Prenatal diagnosis of galactosemia can be made by enzymatic determination in chorionic villusity, in culture of amniocytes or by quantification of galactitol in amniotic fluid. Treatment involves the suppression of galactose in the diet; in new-borns and infants the main source is human and formula milk so these must be suspended and administer soy milk. It is recommended to determine calcium and vitamin D levels and whether supplementation is needed. Galactose 1P should be measured at 3 and 9 months after

initiation of restriction and patients should be checked for language impairments up to 5 years of age [20]. The long-term prognosis appears to be overshadowed by language damage, motor impairment, and ovarian dysfunction. This disease is included in screening programs in many countries. It is common for newborns to present symptoms before having the result of screening, especially in those in which very low enzymatic activity is later demonstrated; when screening includes the determination of the level of galactose in the blood, it is necessary to diagnose the other causes of the increase in galactose in the blood [5]. We propose the following algorithm for the diagnosis of the disease: See Figure 2.

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