

Type I Galactosemia Due to Compound Heterozygous galactose-1-phosphateuridylyltransferase gene variants following a negative initial targeted variant panel in a two-Month-Old Infant: A Case Report

Galactosemia Tipo I por heterocigosis compuesta en galactosa-1-fosfato uridiltransferasa tras panel mutacional inicial negativo en lactante de dos meses: reporte de caso

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Abstract

Introduction: Type I galactosemia is an autosomal recessive inborn error of metabolism caused by a deficiency of the enzyme galactose-1-phosphate uridylyltransferase (GALT). This deficiency leads to the accumulation of toxic metabolites and potentially severe multisystem involvement during the neonatal and early infancy periods.

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Case Presentation: We report a 2-month and 10-day-old female infant with jaundice beginning in the first week of life, severe indirect hyperbilirubinemia, and failure to thrive. Despite an initial suspicion of congenital infection (CMV and EBV), the patient showed no improvement with antiviral therapy and progressed to marked hepatomegaly, severe ascites, and spider nevi.

Diagnostic Evaluation: Laboratory tests revealed macrocytic anemia, thrombocytopenia, and hypoalbuminemia. Expanded newborn screening showed markedly reduced GALT enzymatic activity, while an initial targeted mutation panel was negative. Subsequent molecular sequencing identified compound heterozygosity in the *GALT* gene (c.425T>A; p.Met142Lys and c.292G>C; p.Asp98His), confirming the diagnosis.

Conclusion: Following the initiation of a lactose-free, soy-based infant formula, the patient showed progressive clinical improvement. This case underscores the importance of considering galactosemia in infants with persistent jaundice and progressive hepatic involvement even when initial genetic panels are negative.

Keywords: compound heterozygosity; GALT; hepatomegaly; inborn error of metabolism; failure to thrive; Type I galactosemia.

Resumen

Introducción: la galactosemia tipo I es un error innato del metabolismo de herencia autosómica recesiva causado por deficiencia de la enzima galactosa-1-fosfato uridiltransferasa (GALT), cuya alteración genera acumulación de metabolitos tóxicos derivados de la galactosa y compromiso multisistémico potencialmente grave en el período neonatal y lactante. Su presentación clínica puede simular otras entidades hepáticas o infecciosas, lo que retrasa el diagnóstico si no se mantiene una adecuada sospecha metabólica.

Presentación de caso: lactante femenina de 2 meses y 10 días con ictericia desde la primera semana de vida e hiperbilirrubinemia indirecta severa que requirió hospitalización y transfusión sanguínea. Desarrolló posteriormente distensión abdominal progresiva, edema de miembros inferiores y arañas vasculares, sin mejoría tras manejo antiviral indicado por sospecha inicial de infección congénita. Al ingreso se evidenció hepatomegalia marcada, ascitis severa e hipodesarrollo pondero-estatural.

Evaluación diagnóstica: los estudios de laboratorio mostraron anemia macrocítica, trombocitopenia, hypoalbuminemia y elevación de enzimas hepáticas. El tamizaje neonatal ampliado reveló disminución significativa de la actividad de GALT sin detección de mutaciones frecuentes en el panel inicial. La secuenciación molecular posterior identificó heterocigosis compuesta en el gen GALT (c.425T>A; p.Met142Lys y c.292G>C; p.Asp98His), confirmando galactosemia tipo I.

Conclusión: se instauró dieta libre de lactosa mediante fórmula de soya con tratamiento de soporte, documentándose mejoría clínica progresiva. Este caso destaca la importancia de considerar galactosemia tipo I ante lactantes con ictericia persistente y compromiso hepático progresivo incluso cuando los paneles genéticos iniciales son negativos, y subraya el valor del estudio molecular integral para confirmar el diagnóstico y orientar el seguimiento pediátrico a largo plazo.

Introduction

Galactosemia is an inborn error of metabolism with autosomal recessive inheritance that disrupts the Leloir pathway, which converts galactose to glucose-1-phosphate. Classic galactosemia (Type I) the most severe presentation, is caused by biallelic pathogenic variants in the GALT gene (chromosome 9p13.3)^{1,2}. The resulting loss of enzymatic activity leads to the accumulation of galactose-1-phosphate, galactitol, and galactonate, which cause cellular toxicity affecting the liver, kidneys, lens, and central nervous system.

In settings without early detection programs, the disease presents as a potentially fatal neonatal metabolic emergency^{2,4}. A significant challenge is that 25% to 30% of patients do not carry the common mutations included in standard targeted molecular panels⁵⁻⁸. This report describes the case of a Dominican female infant whose diagnosis was confirmed through comprehensive molecular analysis following a negative initial mutation panel.

Case description

A 2-month and 10-day-old female infant was referred for evaluation due to progressive hepatic involvement and abdominal distension. Symptom onset occurred in the first week of life with persistent jaundice and severe indirect hyperbilirubinemia (22.41 mg/dL), requiring hospitalization and a blood transfusion.

Post-discharge, the infant developed progressive abdominal distension, lower extremity edema, and spider nevi (telangiectasias). She was initially treated with antivirals for presumed congenital cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infection but showed no clinical improvement.

Physical Examination Admission

General: Hemodynamically stable but exhibiting failure to thrive (ponderal and statural undergrowth).

Skin: Pale-grayish skin tone with mildly icteric sclerae.

Abdomen: Distended; liver palpable 10 cm below the right costal margin with spider nevi on the abdominal wall.

Extremities: Bilateral lower extremity edema.



Figure 1. Clinical photographs of the patient demonstrating abdominal distension with spider angiomas upon arrival at the center

Source: medical record.

Diagnostic evaluation

The diagnostic workup was conducted in a stepwise manner, integrating newborn screening, molecular confirmation, biochemical studies, and clinical correlation, in accordance with the recommendations of the *International Clinical Guideline for the Management of Classical Galactosemia*³.

Biochemical Screening

Expanded newborn screening at 2 months and 10 days of age via capillary blood sampling on dried blood spot filter paper (PerkinElmer – StepOne Program), showed a GALT activity of 17 μ M (Reference: >40 μ M). Notably, total galactose levels were within normal limits (4.6 mg/dL), illustrating that enzymatic activity is a more sensitive screening parameter than total serum galactose^{1, 3, 5}.

Molecular Analysis

Etiological confirmation was achieved via buccal cell sequencing, (Prevention Genetics, PGxome method) identifying two heterozygous variants in the GALT gene:

1. c.425T>A (p.Met142Lys): Classified as pathogenic.
2. c.292G>C (p.Asp98His): Classified as likely pathogenic.

The co-occurrence of these variants is consistent with compound heterozygosity for classic galactosemia; however, allelic phase (cis/trans configuration) could not be determined in the absence of parental studies. Additionally, two variants of uncertain significance (VUS) were identified in the *GALM* gene (c.956G>A and c.391C>T), whose clinical relevance remains undetermined in the current context^{3, 5, 6}.

Laboratory findings

Table 1. Complete Blood Count (Admission)

Parameter	Result	Interpretation
Leukocytes	16.110 /μL	Elevated
Neutrophils	36.7%	Diminished
Lymphocytes	54.5%	Elevated
Hemoglobin (Hb)	8.1 g/dL	Anemia
Hematocrit (Hct)	29.7%	Diminished
MCV	117.3 fL — macrocytosis	Elevated
Platelets	90.000 /μL	Thrombocytopenia

Note. Reference values for infants under 12 months.

Source: Hospital Infantil Dr. Arturo Grullón Laboratory.

Table 2. Blood Chemistry (Admission)

Test	Result	Reference Range	Interpretation
Potassium	4.6 mEq/L	3.4–4.5	Mildly elevated
Chloride	103 mEq/L	98–106	Normal
Total bilirubin	6.8 mg/dL	0.1–1.2	Elevated
Direct bilirubin	0.3 mg/dL	0.0–0.2	Elevated
Indirect bilirubin	6.49 mg/dL	≤1.0	Elevated
SGOT (AST)	116 U/L	0–38	Elevated
ALT (SGPT)	43 U/L	15–45	Upper limit of normal
Albumin	2.7 g/dL	3.5–5.0	Hypoalbuminemia
Urea	38.3 mg/dL	15–45	Normal
BUN	17.9 mg/dL	6–21	Normal
Creatinine	0.2 mg/dL	0.7–1.4	Low for age
TP / TPT	Normal	—	Normal

Note. PT: prothrombin time; PTT: partial thromboplastin time.

Source: medical record.

**Figure 2.** Abdominal sonograms with hepatic predominance

Source: medical record.

Therapeutic intervention and follow-up

Following confirmation of the type I galactosemia diagnosis, a lactose-free, soy-based infant formula was initiated. Supportive management included fluid balance maintenance, lactulose, and furosemide for edema control. Micronutrient supplementation (vitamins, zinc, and folic acid) was also provided.

Evolution

7 Months: Ultrasound showed normalization of hepatic size and resolution of ascites, though splenomegaly and mild renal changes persisted.

10 Months: Splenomegaly resolved. The patient demonstrated progressive reduction of jaundice and stabilization of her general condition.

Long-term: The patient requires ongoing longitudinal multidisciplinary surveillance to monitor late complications like cognitive decline or premature ovarian insufficiency.

Discussion

This case highlights the diagnostic challenges in settings without universal expanded newborn screening. The dissociation between GALT enzymatic activity and normal total serum galactose is a recognized source of false negatives in many screening programs^{1, 3, 5, 9}. Furthermore, the initial negative mutation panel illustrates that more than 300 pathogenic variants exist, many of which are not included in common targeted panels^{5, 10}.

The temporal factor is critical; international guidelines mandate that galactose restriction should begin upon suspicion, as delay prolongs exposure during a period of high organ vulnerability^{3, 4, 11}. While dietary restriction reverses acute symptoms, the risk of long-term complications persists regardless of treatment promptness^{2, 4}.

Conclusion

Type I galactosemia should be actively considered in infants presenting with persistent jaundice, hepatomegaly, and failure to thrive, even when total galactose levels are normal and initial mutation panels are negative. Reduced GALT

enzymatic activity is the most sensitive diagnostic trigger. This case documents a favorable outcome through timely dietary restrictions and underscores the urgent need for expanded newborn screening programs.

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