Case Report

Diagnosis of Galactosemia by Simple Technique in a Resource-Constraint Country

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Abstract

Galactosemia is an autosomal recessive inheritance and there is cellular deficiency of enzymes leading to defective/impaired metabolism of galactose resulting in toxic byproducts like galactilol, galactose-1-phosphate and galactonate that affect mainly liver, brain, kidneys, lens and gonads. Galactosemia appears as a rare metabolic cause of neonatal cholestasis syndrome (NCS). The classic disease manifestation after the first milk feeding varies in severity from an acute fulminant illness to a more common subacute illness beginning within the first few days of life. Neonatal sepsis is one of the presentations. Galactokinase deficiency results primarily in cataract formation and galactosuria. The preliminary diagnosis of galactosemia in sick neonates and suspected infants is made by Benedict test in several urine specimens and followed by dipstick test to exclude glycosuria. Gold standard test is demonstration of low enzyme activity in erythrocyte. Galactosemia can be detected by newborn screening methods like the Guthrie test using filter-paper blood samples. Classical form of galactosemia should be treated with an absolute galactose restricted diet without waiting for confirmation of the diagnosis. Here we report a case of a 50-day-old boy with features of neonatal cholestasis, diagnosed as galactosemia by using a simple cost effective method.

Key words*: Neonatal cholestasis; Galactosemia; Benedict test*

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Introduction

Neonatal cholestasis is defined as conjugated hyperbilirubinemia occurring in the newborn within 3 months of life. Galactosemia is one of the important metabolic etiologies.[1] Galactosemia (meaning galactose + blood, accumulation of galactose in blood) is an autosomal recessive inheritance and is expressed as cellular deficiency of enzymes of metabolic pathway of galactose through which galactose is converted into glucose and toxic byproducts like galactilol, galactose-1-phosphate and galactonate that affect mainly liver, brain, kidneys, lens and gonads. These byproducts are produced from galactose in absence or barely detectable deficiency of these enzymes.[2,3] Galactosemia was first discovered by Von Ruess, in 1908[4] but the disease was first recognized and described in details in 1935 by Mason and Turner and the genetic nature of the disease was described in details by Herman Kalckar and co-workers.[5] In 1963,

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Guthrie and Paigen first detected galactosemia through a newborn screening method.[6] It has an estimated incidence of approximately 1:19,000 to 1:44,000 in Europe and the USA with a much higher incidence in Irish travellers (one hundred times more common) for whom the frequency is 1/480[7-11] and an estimated prevalence of one in 23,000–62,000 in western countries.[12,13] Galactosemia appears to account for up to 4% of neonatal cholestasis syndrome (NCS) in India.[14] Galactosemia is found in three distinct forms: (1) Type 1 galactosemia ─ classic and clinical variant/ transferase deficiency is due to deficiency or reduced activity of galactose-1-phosphate uridyltransferase; (2) Type 2 galactosemia ─ galactokinase-deficiency due to deficiency of galactokinase and (3)Type 3 galactosemia ─ epimerase-deficiency due to deficiency of uridine diphosphate (UDP) galactose-4-epimerase.[2] There is another variant named 'Duarte variant galactosemia' which is a milder form of classic type due to the mutation in the GALT gene.[15]

Case report

A 50-day-old boy, 2nd issue of his non-consanguineous parents was admitted in the department of Pediatric Gastroenterology and Nutrition, BSMMU with the complaints of jaundice, dark urine, intermittent pale stool since seven days of his age. Mother's antenatal period was uneventful. Baby was born by LUCS at 36th week with low birth weight and his postnatal event was uneventful. There was no history of delayed passage of meconium, bleeding manifestation, vomiting, lethargy, poor feeding, convulsion, sibling death or family history of such type of illness. On examination he was well alert, icteric, no facial dysmorphism, vitally stable and anthropometrically well-thrived. Bedside urine for reducing substance was brick red (Fig 1) and urine strip test for glucose was negative. On alimentary system examination hepatomegaly (4 cm) was present. Other systemic examinations revealed no abnormality. Laboratory investigations showed direct

Fig 1. Benedict test (brick red) during breast feeding

Fig 2. Benedict test (green) 2 days after withholding breast feeding

Fig 3. Benedict test (blue) 5 days after withholding breast feeding

hyperbilirubinemia, normal prothrombin time and raised serum γ-GT and ALT. Complete blood count and urine culture excluded sepsis. Thyroid function tests were normal, TORCH screening was normal, eye evaluation for cataract, chorioretinitis, posterior embryotoxon, cherry red spot and hypoplasia of optic disc was normal. USG of hepatobilliary system showed contracted gallbladder and hepatomegaly. Hepatobilliary scintigraphy excluded biliary atresia and liver biopsy in favor of neonatal hepatitis (Table I). Urine for reducing substance was positive (brick red) in three samples and urine dipstick test for glucose was negative. Reducing substance in urine other than glucose is considered as galactose or fructose. Hereditary fructose intolerance occurs on exposure to fructose/sucrose and our patient was on exclusive breast feeding, so we excluded possibility of fructose in urine. Metabolic screening for galactosemia was advised but parents were unable to do due to financial problem. So we diagnosed the case as neonatal cholestasis due to galactosemia. We advised mother to stop breast feeding and started lactose free milk. After two days of lactose-free milk, urine for reducing substance was positive but became green (Fig 2) and five days later it was negative (Fig 3). So we finally confirmed the diagnosis as neonatal cholestasis due to galactosemia and continued the lactose-free milk with strict prohibition of breast milk. Two weeks and four weeks after the lactose-free milk periods, liver function tests were repeated and all parameters decreased (Table II).

Table I: Investigations on admission

Investigations with results
Serum bilirubin
Total 12.2 mg/dL
Direct 8.29 mg/dL
Prothrombin time: 14.90 sec
INR 1.21
ALT 317 U/L
γ-GT 820 U/L
CBC Hb% : 13.0 gm/dL ESR : 20 mm in 1st hr WBC: 12,000/cumm D/C: N 46%, L 47%, M 6%, E 1% Platelet: 200000/cu mm
Urine R/M/E Color Straw Reaction Acidic Protein Nil Reducing substance Brick red Pus cell 0–2 /HPF
Urine C/S: No growth
Thyroid function tests TSH: 3.49 µIU/L FT4: 1.62 ng/dL
TORCH screening Anti-Toxoplasma IgM & IgG: Negative Anti-CMV IgM & IgG: Negative Anti-HSV IgM & IgG: Negative Anti-Rubella IgM & IgG: Negative
Ophthalmoscopy evaluation: No abnormality found
USG of hepatobilliary system: Mild hepatomegaly with contracted gallbladder
Hepatobilliary scintigraphy: Uptake of radiotracer is poor but excretion occurs in lumen of intestine within 24 hours.
Liver biopsy: Liver architecture is distorted. Chronic inflammatory cell infiltration and giant cell transformation is present. No bile ductular proliferation.
Metabolic screening for galactosemia – not done due to financial problem

Table II: Investigations on follow-up

Investigations 2 weeks after the lactose-free milk	
Serum total bilirubin	5.5 mg/dL
Prothrombin time	12.90 sec
INR	1.06
ALT	68 U/L
Urine for reducing substance	Negative
Investigations 4 weeks after the lactose-free milk	
Serum total bilirubin	1.9 mg/dL
Prothrombin time	12 sec
INR	1.01
ALT	36 U/L
Urine for reducing substance	Negative

Discussion

Conjugated hyperbilirubinemia in a newborn is defined as a serum direct (conjugated) bilirubin concentration greater than 1.0 mg/dL if the total serum bilirubin (TSB) is <5.0 mg/dL or greater than 20% of TSB if the TSB is >5.0 mg/dL.[1]

In our case, direct bilirubin was 8.29 mg/dL which was 68% of total bilirubin. In galactosemia, the classic disease manifestations start after the first milk feeding, varies in severity from an acute fulminant illness (characterized by abdominal distension, vomiting, diarrhea, anorexia and hypoglycemia) to a more common subacute illness (such as jaundice and failure to thrive) beginning within the first few days of life.[2]

Other manifestations like jaundice, hepatomegaly, vomiting, hypoglycemia, seizures, lethargy, irritability, feeding difficulties, poor weight gain, aminoaciduria, nuclear cataracts, vitreous hemorrhage, hepatic failure, liver cirrhosis, ascites, splenomegaly, or intellectual disability are usually present.[16] Our patient had hepatomegaly and jaundice since seven days of life.

Neonatal sepsis is one of the presentation and E. coli associated sepsis has a direct correlation with galactosemia[17], but other organisms like Klebsiella, Staphylococcus, β-hemolytic streptococci and Streptococcus fecalis may cause sepsis.[13] Our case had no feature of sepsis.

Galactokinase deficiency primarily results in cataract formation and galactosuria. In most cases of epimerase deficiency, the disease is mild and affected individuals display no clinical or laboratory manifestations of galactosemia. In a variant form of epimerase deficiency galactosemia identified by Holton and colleagues in 1981, the defect is more generalized and results in a severe clinical presentation resembling the classic form of the disease.[2] Our case had no cataract but galactosuria was present.

The preliminary diagnosis of galactosemia in sick neonates and suspected infants is made by demonstrating reducing substance in several urine specimens (Benedict test) collected while the patient is receiving human milk, cow's milk, or any other formula containing lactose and followed by dipstick test to exclude glycosuria (Clinistix test/Clinitest).[16] In our case Benedict test was positive (brick red) in three samples and urine dipstick test for glucose was negative.

Confirmatory diagnosis is made by demonstration of low enzyme activity in erythrocyte which is gold standard, but before that patient should be free from any blood transfusion prior to the test. Demonstration of high levels of galactose and galactilol in urine by gas chromatography is also diagnostic.[2,13] Various newborn screening methods for galactosemia are available. The Guthrie test uses filter-paper blood samples from which a microbiologic assay detect elevated galactose levels.[2] Metabolic screening for galactosemia was advised, but parents were unable to do due to financial problem.

Classical form of galactosemia should be treated with an absolute galactose-restricted diet. As soon as galactosemia is strongly suspected, immediately a galactose-restricted diet like, soy-based, casein hydrolysate (pregestimil, nutramigen) and the soy-bean milk preparations or elemental formula should be commenced without waiting for confirmation of the diagnosis. For most infants, the galactose-restricted diet includes discontinuation of breast milk or whey-based infant formulas and initiation of a soy-based formula, but an elemental formula may also be chosen.[18] In our case we immediately stopped breast-feeding and started lactose-free formula milk.

Casein hydrolysate formulas, containing medium-chain fatty acids, may be beneficial for infants with significant liver disease. Due to the high galactose content of all animal milks and other dairy products (cow's milk contains 2400 mg galactose/100 mL), and elimination of dairy products from the diet, patients with galactosemia are at risk for calcium and vitamin D deficiency. Both calcium and vitamin D should be supplemented.[2,19] In our case we gave supplemental calcium.

Elimination of galactose from the diet along with adequate calcium supplementation reverses growth failure, renal and hepatic dysfunction. Cataracts regress and most patients have no impairment of vision.[16] In our case liver function was improved after treatment.

Measurement of red blood cell Gal-1-P levels should be done at diagnosis, at three and nine months in the first year of life of dietary galactose restriction and then yearly until an individual baseline has been established.[19] Despite full restriction of galactose-free diet some long term complications like (i) cataract, (ii) learning disability and developmental delay, (iii) neurological impairment like ataxia, tremor, dysmetria, (iv) speech disorder, (v) ovarian failure with primary or secondary amenorrhea, (vi) decreased bone mineral density and (vii) hypergonadotropic hypogonadism are reported in 80% to more than 90% of female patients with classic galactosemia.[19] Treatment of galactosemic patients with a galactose-free diet results in survival with reversal of the acute symptoms, normal growth, and complete recovery of liver function. However, the long-term outcome (particularly for intellectual development) is not entirely certain.[13] In our case, on follow-up there was no cataract and symptoms were resolved.

When untreated, galactosemia results in early deaths of many affected children and is attended by the prospect of mental retardation of those who survive.[2] Most important indicator of morbidity and mortality in patients with galactosemia is E.coli-mediated sepsis and fulminant hepatic failure.[13] Our case was infection-free during hospital course and follow-up.

Conclusion

As a metabolic cause of neonatal cholestasis, galactosemia can be detected very early by doing a cheap, bedside routine Benedict test which helps to halt the disease progression at early stage and minimize complication in less-facilitated institution and country. Treatment of galactosemic patients with a galactose-free diet results in survival with reversal of the acute symptoms, normal growth, and complete recovery of liver function but the long-term outcome is not entirely certain.

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