

## Case Report

# Galactosemia Presenting as Recurrent Sepsis

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### Summary

Galactosemia is a treatable metabolic disorder caused by the deficiency of enzyme galactose-1-phosphate uridyl transferase (GALT) and inherited as an autosomal recessive trait. A case of neonate manifesting with recurrent *Escherichia coli* sepsis is presented here which turned out to be a classic galactosemia. No other common presenting features were observed in this infant except cataract on slit lamp examination. To the best of our knowledge, there is no case of galactosemia reported in literature which presented with recurrent neonatal sepsis without hepatomegaly, hyperbilirubinemia, bleeding disorder, vomiting, diarrhea, failure to thrive, hypoglycemia, coagulopathy, hemolysis or renal tubular acidosis.

**Key words:** galactosemia, recurrent sepsis, cataract, GALT.

### Introduction

Galactosemia, elevated levels of galactose in the blood, is found in three disorders of galactose metabolism defective in one of the enzymes; galactose-1-phosphate uridyl transferase (GALT), galactokinase and epimerase. The term galactosemia, although adequate for any of these three disorders, generally denotes GALT deficiency [1]. The incidence of galactosemia is variously quoted as 1:60 000 to 1:10 000 [1, 2]. The diagnosis of galactosemia should be considered in newborn or young infant with any of the following features; failure to thrive, jaundice, hepatomegaly, vomiting, hypoglycemia, convulsions, cataracts, bleeding diathesis, renal tubular acidosis, hepatic cirrhosis and mental retardation. The infants with galactosemia are at increased risk for *Escherichia coli* neonatal sepsis. If a galactose-restricted diet is initiated during the first 3–10 days of life, the symptoms resolve quickly and prognosis is good for prevention of liver failure, *E. coli* sepsis, neonatal death and mental retardation. In developed countries, early diagnosis of galactosemia is made by

routine newborn screening programs. However, newborn screening is not widely available in many developing nations and the galactosemia is diagnosed only if clinically suspected. We report a case of neonate who presented with recurrent neonatal sepsis but without any other common presenting features of galactosemia.

### Case Report

A 25-day-old male neonate, born out of second degree consanguineous marriage, presented with history of feeding difficulty and lethargy of 4 days duration. There was no history of vomiting, diarrhea, fever, umbilical discharge, rash, coryza or cough. The infant was born by vaginal delivery and was exclusively breastfed. His birth weight was 2.5 kg. The perinatal history course was uncomplicated and infant was appropriately immunized for his age. His elder sister was 5 years old and normal. On examination, he was lethargic with poor suck and sluggish neonatal reflexes. There was no icterus, hepatomegaly and bleeding tendencies. There was no hypotonia and the auditory startle was normal. His weight on admission was 2.8 kg.

Investigations revealed hemoglobin of 12.6 g dl<sup>-1</sup>, WBC 19 900 mm<sup>-3</sup>, polymorphs 78%, lymphocytes 20%, monocytes 2%, reticulocyte count 1% and C-reactive protein 43 mg l<sup>-1</sup>. The blood glucose, serum calcium, cerebrospinal fluid studies, urine

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analysis, liver profile and serum chemistry were normal. The diagnosis of neonatal sepsis was made, blood culture was sent and intravenous cefotaxime ( $100 \text{ mg kg}^{-1} \text{ day}^{-1}$ ) and amikacin ( $15 \text{ mg kg}^{-1} \text{ day}^{-1}$ ) started. The infant responded well to the treatment, became active and started accepting feeds from third day of antibiotic therapy. The blood culture grew *E. coli* sensitive to cefotaxime and amikacin. He received 14 days of antibiotic therapy. On discharge, he was 2.8 kg, clinically normal with WBC of  $8000 \text{ mm}^{-3}$  and CRP  $5 \text{ mg l}^{-1}$ . He remained well at home for next 3 weeks and developed social smile. The infant was re-admitted with poor feeding and lethargy of 3 days duration. He looked sick without any obvious focus of infection and weighed 3.3 kg. There was no hepatomegaly, jaundice, ascitis, vomiting or diarrhea. The laboratory tests were suggestive of septicemia with Hb  $12 \text{ g dl}^{-1}$ , WBC  $29000 \text{ mm}^{-3}$ , polymorphs 75%, lymphocytes 23%, monocytes 2%, reticulocyte count 1% and CRP  $61 \text{ mg l}^{-1}$ . The serum chemistry, cerebrospinal fluid studies, urine analysis, chest X-ray, abdominal ultrasound, liver and coagulation profile and arterial blood gas was normal. The blood culture was sent and the infant was treated with intravenous piperacillin-tazobactam ( $300 \text{ mg kg}^{-1} \text{ day}^{-1}$ ) and intravenous ceftriaxone ( $100 \text{ mg kg}^{-1} \text{ day}^{-1}$ ). The infant responded well to antibiotic therapy and blood culture grew *E. coli* sensitive to cefotaxime, ceftriaxone, piperacillin and amikacin.

As there was no obvious cause for the recurrent sepsis in this infant, a possibility of galactosemia was entertained. Urine benedicts test was performed which was positive for reducing substance (1.5%) without glucosuria. The blood and urine samples were sent for metabolic tests. The ophthalmoscopy was normal but the slit lamp examination of the eyes revealed cataracts in both the eyes. The thin layer chromatography on urine revealed galactose 3+. The total blood galactose was  $75.8 \text{ mg dl}^{-1}$  (normal value  $<15 \text{ mg dl}^{-1}$ ) and the GALT was low 0.62 U gram per hemoglobin (normal value  $>2.4 \text{ U gram per hemoglobin}$ ). The diagnosis of galactosemia was made, the breast feeding was completely stopped and the infant was fed lactose-free diet. He was discharged after completing 14 days of intravenous antibiotic therapy. The infant is 3 months old now and doing well. He achieved social smile at 9 weeks and has no neck control at present.

### Discussion

Galactosemia is an inherited metabolic disorder and if not diagnosed early, can lead to significant mortality and morbidity. The infants with galactosemia presents with failure to thrive, jaundice, hepatomegaly, vomiting, hypoglycemia, convulsions, cataracts, bleeding diathesis, renal tubular acidosis, hepatic cirrhosis and mental retardation. However, we are

reporting an unusual case of galactosemia, which presented with the recurrent *E. coli* sepsis without any other clinical features of galactosemia except cataract on the slit lamp examination.

There are three congenital disorders related to galactose metabolism.

1. Type I galactosemia (Classic galactosemia): deficiency of GALT.
2. Type II galactosemia: deficiency of enzyme galactokinase. Presents solely with cataracts.
3. Type III galactosemia: deficiency of enzyme UDP-galactose-4-epimerase. This type has two forms: benign and severe. Benign form is asymptomatic and needs no treatment. Severe form presents as classic galactosemia in children, but they additionally have deafness and hypotonia. It is suspected in children with features of classic galactosemia having normal GALT activity.

There is significant heterogeneity seen in classic galactosemia. Homozygotes for classic galactosemia(G) allele (G/G) have GALT enzyme activity  $<5\%$  of control values, while heterozygotes for classic galactosemia allele and a normal (N) allele (G/N) have GALT activity that is 50% of control values. In 'Duarte' variant, there is structural and functional abnormality leading to instability of GALT. Using D for Duarte allele, D/N, D/D and D/G genotypes were proposed which showed 75%, 50% and 25% of normal GALT enzyme activity, respectively [3].

Failure to thrive is the most common initial presenting symptom of galactosemia [4].

But this feature was absent in our patient. Waggoner *et al.* [5] in a study of 350 cases of symptomatic galactosemia found hepatocellular damage (jaundice, hepatomegaly, abnormal liver function tests, coagulation disorder, ascitis) in 89% cases and feeding intolerance (vomiting, diarrhea) in 76% cases. Bozkowa *et al.* [6] in a study of 17 galactosemic children described hepatomegaly in 94%, jaundice in 81%, splenomegaly in 79%, vomiting in 62% and diarrhea in 56% cases. Henderson *et al.* [7] in a review of nine galactosemia patients described hepatomegaly in 100% and splenomegaly, failure to thrive, developmental delay in 66% patients. Our case was unique in that all these features were absent in our patient. Other clinical features of galactosemia like hypoglycemia, seizures, hemolysis and renal tubular acidosis were also not seen in our case. Sepsis is described in 10–50% of symptomatic galactosemia patients [5, 8]. *Escherichia coli* is the most common organism but organisms like Klebsiella, Enterobacter, Staphylococci,  $\beta$ -streptococcus and *Streptococcus faecalis* are also known to cause sepsis in patients with galactosemia. The patients with galactosemia are prone to sepsis due to inhibition of leucocyte bactericidal activity secondary to impairment of cellular release of superoxide

ion by galactose [9]. Establishing a diagnosis of sepsis does not exclude the possibility of galactosemia, as sepsis, particularly *E. coli* sepsis occurs commonly in infants with galactosemia. There appears to be a high frequency of neonatal deaths because of *E. coli* or other Gram-negative sepsis [8]. The diagnosis of galactosemia should be suspected in any infant presenting with *E. coli* sepsis. We should have screened our patient for galactosemia during the first episode of *E. coli* sepsis. Onset of sepsis often precedes the diagnosis of galactosemia [1, 7]. But these patients usually have other clinical features of galactosemia. Bacterial infections among galactosemic neonates generally seem to develop at the end of first week or during the second week of life [8], but our case was exceptional in that sepsis developed in fourth week of life.

The incidence of cataracts in patients with galactosemia is variously reported at 38–66% [6, 7]. The cataract can be detected only on slit-lamp examination and missed with an ophthalmoscope [4], as seen in our case. The diagnosis of galactosemia is established by the measurement of erythrocyte GALT enzyme activity. The molecular testing is also available. In developed nations, galactosemia is diagnosed with the newborn screening program. The prenatal testing is available for at-risk siblings. The infants with galactosemia are treated with galactose- and lactose-free diet, calcium supplements, avoiding medicines containing lactulose and periodic follow-up for ophthalmological examination, developmental evaluation, speech assessment and accumulation of toxic metabolites (RBC galactose-1-phosphate, urinary galactitol). With the early diagnosis and the institution of galactose-free diet, complications of liver failure, sepsis, neonatal death and mental retardation can be prevented. In spite of adequate treatment from the early age, these children have increased risk of developmental delay, speech problem, abnormalities of motor function and premature ovarian failure [10]. Galactose-free diet should continue throughout life, though managing diet becomes less important after infancy when milk and dairy products are no longer the primary source of energy. It is debated as to how stringent the diet should be after the first year of life as endogenous galactose production is in order of magnitude higher than that ingested from foods other than milk [11, 12].

The authors conclude that galactosemia should be suspected in every infant presented with *E. coli* sepsis even if other clinical features of galactosemia are absent. This is important in developing countries where the newborn screening is not routinely

performed for early diagnosis of galactosemia. As neonates with galactosemia present with *E. coli* sepsis in first and second weeks of life, results from the newborn screening may not be available. It is important to keep high index of suspicion to diagnose galactosemia as early treatment has significant impact on the outcome of this disease. Every neonate with *E. coli* sepsis should be screened for galactosemia by testing reducing substance and glucose in urine. The slit lamp examination of the eyes should be done as cataract could be missed by simple ophthalmoscopy.

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