CASE REPORT

Galactosaemia: an unusual cause of chronic bilirubin encephalopathy

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SUMMARY

Galactosaemia is a disorder of galactose metabolism in which raised levels of galactose and galactose-1-phosphate damage various organs. Although galactosaemia is a common metabolic liver disease in childhood, it is a rare cause of neonatal hyperbilirubinemia requiring intervention. We report an unusual case of neonatal galactosaemia that at presentation had features of acute bilirubin encephalopathy requiring exchange transfusion and at discharge had features of chronic bilirubin encephalopathy. This case report emphasises the need for timely suspicion and diagnosis of this disease for prevention of chronic morbidity.

BACKGROUND

Galactosaemia is a rare autosomal recessive disease (incidence 1 in 60 000 worldwide)¹ in which galactose is not properly metabolised, resulting in accumulation of toxic metabolites in the tissues. Dietary lactose is broken down by lactase into glucose and galactose and then, in a three-step process, galactose is converted to glucose. This metabolic pathway is particularly important for the newborn, whose main carbohydrate source is lactose (up to 40% in breast milk and in certain formulas). Any delay in diagnosis can result in irreversible damage to various organs. Prevention of death or permanent neurological sequelae is dependent on early diagnosis and institution of appropriate therapy.² Although several countries have included galactosaemia in their universal neonatal screening programme,^{3–6} in developing countries such as India, it has not yet been implemented. Owing to lack of inclusion in national screening programmes, exact incidence of galactosaemia in India is not known. We report a case of a neonate with galactosaemia who at admission presented with acute bilirubin encephalopathy and required double volume exchange transfusion. To the best of our knowledge, it is the first ever reported case of acute and chronic bilirubin encephalopathy occurring due to galactosaemia.

CASE PRESENTATION**Case profile**

We present a case of a 7-day-old male neonate, born at home with the aid of a traditional birth attendant to a 28-year-old second gravida mother with no history of consanguinity. The mother had one previous healthy child and had an apparently uneventful antenatal period with no history of neonatal jaundice in the first sib. The present case was

brought with a history of jaundice, poor feeding for 48 h and multiple episodes of multifocal clonic seizures over 160 h of life.

The baby had started taking breast feed immediately after birth and remained well until 72 h of life, when his mother noticed a yellowish discolouration of his body. This was presumed by the family to be clinically insignificant and no advice was sought. The neonate was observed at home for the subsequent 4 days until the episode of abnormal movement occurred, after which the neonate was shifted to the hospital.

Examination details

At admission, the neonate was found to be deeply icteric, pale, obtunded and intermittently irritable. Neurological examination revealed lethargy, poor response to surroundings, absence of cranial nerve palsy, presence of appendicular and truncal hypotonia and a poor suck. The infant had hung up Moro reflex (incomplete Moro reflex with no adduction and anterior flexion). Systemic examination revealed no evidence of cataract, hepatosplenomegaly or skin bleeds and was otherwise also unremarkable. There was no evidence of clinical coagulopathy in the form of prolonged puncture site bleed, altered aspirate or skin bleeds.

DIFFERENTIAL DIAGNOSIS

A clinical possibility of late onset neonatal sepsis and meningitis were considered initially and investigations were made accordingly.

INVESTIGATIONS

Total serum bilirubin value was 50 mg/dL (855 μ mol/L (SI)), performed using Diazo method (Roche Diagnostic Kit, Germany), with direct bilirubin level being 20 mg/dL (340 μ mol/L (SI)). Liver function tests were deranged (aspartate transaminase of 93 IU/dL (normal range up to 50 IU/dL), alanine transaminase of 65 IU/dL (normal up to 50 IU/dL) and alkaline phosphatase of 550 IU (normal value up to 240–840 IU/dL)). Blood sugar value was normal. Cerebrospinal fluid examination was normal and sepsis screen was negative (total leucocyte count (TLC) 14 500/ mm³, absolute neutrophil count (ANC) 6500/ mm³; erythrocyte sedimentation rate (micro-ESR) 10 mm in first hour, C reactive protein (CRP) negative, immature to total neutrophil (IT) ratio 0.3 (TLC <5000/ mm³, ANC < norms specific for age, micro-ESR >15 mm fall first hour, CRP positive, IT ratio >0.2); any two of the above five parameters suggest a positive screen); and blood culture was sterile.⁷

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Peripheral smear suggested no evidence of haemolysis. Haemoglobin value was 12 g/dL with reticulocyte count of 2% and glucose-6-phosphate dehydrogenase screen was normal. Mother and baby were both B+ve blood group. Direct Coomb's test was negative (for major as well as minor blood group incompatibility), and the IgM and IgG antibody levels examined for toxoplasmosis, cytomegalovirus in the mother and the neonate were normal. Peripheral smear for malaria was also negative.

Urine examination for succinyl acetone was negative. The thyroid profile was normal. Urine for reducing substances was positive and the blood subsequently sent for the enzyme levels of galactose-1-phosphate uridyl transferase revealed deficient enzyme levels (2 $\mu\text{mol/h/mL}$: normal 4–12 $\mu\text{mol/h/mL}$).

MRI performed on day 11 of life revealed bilateral hyperintensities in bilateral globus pallidus in a T2-weighted image, suggesting acute bilirubin encephalopathy (figure 1).

TREATMENT

In view of clinical acute bilirubin-induced neurological damage, the neonate underwent double volume exchange transfusion followed by intensive phototherapy for 60 h and phenobarbitone for seizure control. The neonate was started on lactose-free infant formula (available in the local market) and multivitamin supplement.

OUTCOME AND FOLLOW-UP

At the time of discharge on day 23, the neonate had features of chronic bilirubin encephalopathy in the form of a poor suck, axial hypotonia with normal appendicular tone and hung up Moro reflex. Brain stem-evoked response audiometry revealed bilateral impaired hearing. The neonate was discharged on lactose-free formula with vitamins A, D, E and K supplementation (for hepatic involvement).

On follow-up at 3 and 12 months, the infant continued to have extrapyramidal symptoms in the form of dystonia, sensory neural hearing loss, global developmental delay with DQ 40–50 (indicating severe delay: normal DQ level ≥ 85) and microcephaly (in WHO MGRS growth chart for head circumference,

value was less than 3rd centile).⁸ He was continued on lactose-free formula and genetic counselling was given to the parents for a decision on future pregnancy. The family was referred for a hearing aid for their child.

DISCUSSION

Galactosaemia is a common metabolic liver disease of childhood including during the neonatal period. Although galactosaemia is due to a defect in either galactose-1-phosphate uridyl transferase, galactokinase or uridine diphosphate galactose-4-epimerase, the term *galactosaemia*, in most cases, denotes classical galactosaemia involving transferase deficiency. According to age of presentation, classic galactosaemia can be divided into two forms: infants with complete or near complete deficiency of the enzyme (classic galactosaemia) and those with partial transferase deficiency with a relatively benign course of onset.⁹ Classic galactosaemia, which presents mostly in the second half of the first week of life, is due to excessive accumulation of galactose-1-phosphate and other precursors, causing damage to many vital organs such as the kidneys, liver and brain. Diagnosis should be considered in any newborn with jaundice, hepatomegaly, vomiting, hypoglycaemia, seizures, lethargy, irritability, feeding difficulties and cataract. Although theoretically, galactosaemia can cause acute bilirubin encephalopathy and chronic bilirubin-induced neurological damage in severe untreated cases, literature supporting this is sparse. The neurological features of acute bilirubin-induced encephalopathy can be divided into two phases: the initial phase occurs in the first few days of life and is characterised by somnolence, hypotonia and loss of Moro reflex, fever and high-pitched crying; the second phase causes irreversible changes such as retrocollis and opisthotonus, while features of chronic bilirubin encephalopathy include extrapyramidal movements, sensorineural hearing loss, dental dysplasia, gaze abnormalities and mild mental retardation.¹⁰ Our index case had lethargy, hypotonia and hung up Moro reflex in the acute stage, and global developmental delay, sensory neural hearing loss and dystonia in the chronic stage.

The diagnosis of galactosaemia is generally suspected by demonstrating a reducing substance in repeated urine specimens while the patient is receiving human milk, cow's milk or any other formula containing lactose. Direct enzyme assay using erythrocytes is the gold standard for diagnosis of galactosaemia. In our index case, galactosaemia was suspected by positive urine-reducing sugar and it was confirmed by enzymatic assay.

Implementation of a newborn screening programme in several countries^{3–6} has made it possible to detect galactosaemia, in a timely fashion, in many neonates who would have otherwise been missed and would have presented in later stages with irreversible organ damage.⁹ This is important because elimination of galactose from the diet reverses growth failure, and renal and hepatic dysfunction; also, cataracts regress and most patients have no impairment of vision, although on long-term follow-up many patient may have developmental delay, language disability, learning disability (present in most of the patients) and ovarian failure. Our index case had global developmental delay on follow-up, which can be directly attributed to galactosaemia, while sensory neural deafness and choreoathetoid movements can be due to kernicterus secondary to hyperbilirubinemia.

Early diagnosis and subsequently early treatment certainly improves the prognosis in galactosaemia. Unfortunately, in a populous country such as India, which contributes to the largest galactosaemic load in the world,¹¹ universal screening is still not implemented. Although recently launched national programmes have identified many metabolic diseases for screening, such as

Figure 1 T2-weighted MRI of the brain suggestive of bilateral globus pallidus hyperintensities.

congenital hypothyroidism, they do not include screening for neonatal galactosaemia due to financial constraints.

Most of the available literature on galactosaemia suggests hyperbilirubinemia due to galactosaemia is predominantly conjugated (a direct acting type),^{12 13} suggesting a primary hepatic origin. Some recent evidence indicates the predominance of unconjugated hyperbilirubinemia in galactosaemia, especially when manifesting early in life,^{14 15} although the exact aetiology is still unclear. One possible hypothesis is that this is due to intravascular haemolysis secondary to accumulation of galactose-1-phosphate inside RBCs.¹⁶ Previous data suggest that of the total cases of conjugated hyperbilirubinemia, nearly one-fifth are due to metabolic liver disease, but the percentage contributed by galactosaemia is still not known.¹⁷ Worldwide prevalence of kernicterus following extreme hyperbilirubinemia or Rh haemolytic disease is 73/100 000 live births out of which south Asia contributes 37% of cases.¹⁸ To the best of our knowledge, this is the first ever reported case of neonatal galactosaemia causing bilirubin encephalopathy leading to residual neuromorbidity.

Learning points

- Galactosaemia can be a cause of acute bilirubin encephalopathy.
- An infant diagnosed to be suffering from galactosaemia should be observed for jaundice and serial monitoring of serum bilirubin (conjugated as well as unconjugated) is warranted.
- Cost effectiveness of including galactosaemia in national neonatal screening programmes in developing countries should be seriously re-evaluated and prompt action taken.

Contributors TS and AT worked up, managed and followed the case, and wrote the manuscript. RA and MJS collected the literature and drafted the manuscript.

Competing interests None.

Patient consent Obtained.

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