

## A case of misdiagnosis of classical galactosemia - Role of genetic analysis in making correct diagnosis

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**Abstract:** Galactosemia is an autosomal recessive disorder caused by deficient or absent activities of one of the three enzymes involved in the galactose metabolic pathway. The predominant form is classic type galactosemia caused by severe reduction or absence of the galactose-1-phosphate uridyl transferase (GALT) enzyme. We report on a case of classical galactosemia where the diagnosis was masked by the presence of non-specific manifestations suggesting lactose intolerance. Genetic analysis of the index patient for galactosemia revealed presence of Q188R mutation in exon 6 of GALT gene in heterozygous state. This case exemplifies the problems faced in reaching a correct diagnosis in patients with metabolic diseases demonstrating the importance of molecular genetics in correctly identifying galactosemia which may be lifesaving as treatment simply involves instituting a galactose free diet throughout life.

**Keywords:** Galactosemia, lactose intolerance, mutation, galactose-1-phosphate uridyl transferase (GALT)

### INTRODUCTION

Classical galactosemia is an inherited recessive disorder of galactose metabolism caused by deficiency of the enzyme galactose-1-phosphate uridyl transferase (GALT) [1-4]. As with other metabolic disorder, the clinical presentation of galactosemia is often non-specific and may mimic other diseases. It is not uncommon that patients with metabolic disorders are not correctly recognized and that there is a substantial delay between onset of clinical manifestations and diagnosis. In this communication, we present a case of classical galactosemia illustrating the complications faced in achieving a correct diagnosis when clinical manifestations were non-specific and non-indicative of a particular disorder.

### CASE REPORT

A 20-day male infant born to non-consanguineous parents was admitted to the neonatal ward of our hospital with a history of jaundice since birth and abdominal swelling for a few days. Baby was passing high colored urine and clay colored stools and had recurrent vomiting. He had been feeding well on breast milk until a few days earlier when he started tiring during feeds but without sweating or cyanosis. No bleeding tendencies or rashes were reported.

Physical examination disclosed a distended abdomen and superficial prominent venous pattern was

visible. The weight was 3.25 kg, length was 50 cm, and occipitofrontal circumference was 32.8 cm. Eye examination did not show any cataracts. There was no hepatosplenomegaly. Biochemical investigations showed normal blood cell and reticulocyte counts. Liver function tests showed aspartate and alanine transaminase of 31 U/L and 59 U/L, respectively (normal range: 15–45 U/L). The total serum bilirubin was 9.2 mg/dL. The serum alkaline phosphatase was 641 IU/L (range: 20–250 IU/L). The coagulation profile revealed a prothrombin time of 18s (normal range 10–15s), activated partial thromboplastin time of 58s (normal range 31–54s), and an international normalized ratio of 1.58.

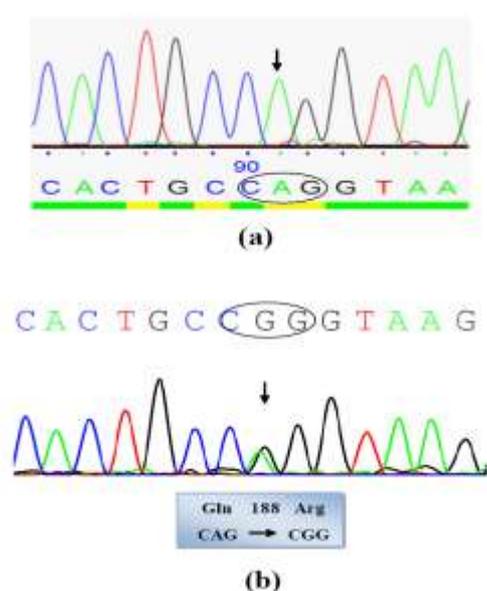
A hypothesis for lactose intolerance was made on the basis of recurrent vomiting. The child was put-off from breast feeding and shifted to a low-protein, lactose-free, hydrolysate formula for 10 days, until the age of 30 days. He made progressive clinical improvement and recovered completely from the biochemical abnormalities. He was kept on lactose free diet and discharged from the hospital.

At the age of 1.5 months, standard formula feeding was re-introduced along with intermittent breast feeding. The child was also given supplementary oral lactase enzyme to aid in the lactose absorption. To our surprise, he was again admitted to our hospital at age of

2 months and presented with jaundice and recurrent vomiting. The child looked lethargic and emaciated. There was hepatomegaly (liver was 5 cm below right costal margin with a span of 10.5 cm) and splenomegaly (4 cm under left costal margin). The total serum bilirubin was found to be 8 mg/dl. The aspartate and alanine transaminase levels were 30 U/L and 55 U/L (normal range: 15–45 U/L), respectively, while serum alkaline phosphatase was 527 IU/L (range: 20–250 IU/L). The prothrombin time was 14s and activated partial thromboplastin time was 37s with an international normalized ratio of 1.05. Virology study for congenital infections – toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus (TORCH screen) was negative.

In view of cholestasis, galactosemia was suspected and the child was evaluated for same. A significantly reduced GALT activity of 11% was observed (normal  $\geq 50\%$ ) [1-5]. Further, genetic analysis revealed the presence of Q188R mutation in heterozygous state in exon 6 of the GALT gene (Figure 1) which confirmed the diagnosis of galactosemia.

The patient was managed with appropriate supportive and nutritional care along with cessation of breast feeding whilst soya-milk formula was initiated. His general condition progressively became better and he was discharged from the hospital after 18 days on appropriate dietary advice and multivitamin supplementation. At 5 months of follow-up, the infant is passing normal colored stools and is anicteric and gaining weight, although at a slower pace.



**Fig- 1: Electrophoregram showing the - (a) Wild type GALT sequence (b) GALT gene sequence depicting substitution of A to G at nucleotide position 563 resulting in glutamine to arginine change at codon 188 in heterozygous state**

## DISCUSSION

We present a case of a neonate with a non-specific presentation of vomiting, failure to thrive, lethargy, and prolonged jaundice. This case emphasizes the importance of thinking to rare metabolic disorders in the differential diagnosis of patients presenting with relatively non-specific symptoms.

On the basis of a large number of biochemical and clinical observations, it is evident that galactosemia can manifest in a variety of clinical pictures [6]. In our patient, diagnosis of galactosemia was delayed due to the presence of non-specific symptoms because of which a misdiagnosis of lactose intolerance was made initially. Further, the absence of cataracts, a typical finding of galactosemia, added to the delay of suspecting and achieving correct diagnosis of galactosemia. The diagnosis of galactosemia is usually made by evaluating the GALT enzyme activity in peripheral RBCs. However, this should always be confirmed with the molecular diagnosis to avoid the false negative or false positive results arising from biochemical diagnosis [7]. Since, in one of our previous studies, we have identified Q188R and N314D to be the most common GALT gene mutation present in the Indian population [1-3], we evaluated our patient for these mutations. The Q188R mutation, found in a heterozygous state, in our patient is caused by a c.563a>g transition in exon 6 (Figure 1) and is located in a highly conserved region of the GALT gene [8-9].

This case demonstrates how correctly identifying galactosemia may be lifesaving as treatment simply involves instituting a galactose free diet throughout life [10]. It also highlights the heterogeneity of classical galactosemia and emphasizes the importance of genetic analysis in diagnosis of galactosemia. Further, because the results of genetic testing are independent of the onset of symptoms, DNA analysis for most common mutations in the GALT gene can be used as a screening procedure for an early diagnosis of galactosemia. Unfortunately, we don't have galactosemia included in the newborn screening program in India.

## CONCLUSION

Every newborn with unexplained clinical manifestations like vomiting, diarrhea, weight loss, lethargy, hypotonia, jaundice, hepatomegaly, *E. coli* sepsis, cataracts, bleeding tendencies and liver failure should be suspected of having an inherited error of intermediary metabolism since a substantial number of these diseases respond well to treatment but may otherwise be fatal.

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#### **Conflict of interest**

The authors declare no conflict of interest.

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