Classic Galactosemia: Indian Scenario

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Classic galactosemia is an autosomal recessive disorder of galactose metabolism due to deficiency of the enzyme galactose-1-phosphate uridyltransferase (GALT). Most affected babies develop severe manifestations such as failure to thrive, vomiting, diarrhea, hypoglycemia, hypotonia, jaundice (which is often unconjugated in the beginning) and cataracts within 1-2 weeks of starting milk feeding [1,2]. Without treatment, these babies progress to severe liver disease (hepatosplenomegaly, abnormal liver function tests, coagulopathy, cirrhosis, ascites), renal tubular damage and brain damage. Often they develop life threatening bacterial sepsis, most commonly due to *E. coli* infections. Fatality is high in untreated cases. However, response to withdrawal of galactose (milk) is almost dramatic in most cases – acute symptoms subside within a few days and liver functions improve rapidly to full recovery [1,3]. Nevertheless, long term outcome is somewhat frustrating, as despite early diagnosis and strict dietary therapy, many, inevitably demonstrate long-term complications such as cognitive and motor dysfunction, speech and learning difficulties (>70%), osteoporosis and hypogonadism with infertility (> 90% females) [4,5].

Galactosemia has a reported incidence of 1:30,000 to 1:60,000 in western countries [6]. Not much is known of the disease in India and published literature on the subject is scanty [7-9]. Galactosemia appears to account for upto 4% of neonatal cholestasis syndrome (NCS) in India [10]. In this issue of *Indian Pediatrics*, Sen Sarma, *et al*. [11] describe clinical features and outcome of a series of children diagnosed with galactosemia during the years 2003 to 2014 at the Pediatric Gastroenterology unit of SGPGI, Lucknow. All children in this series were essentially referred cases of NCS, and diagnosed as galactosemia through investigative protocols of NCS. The age at diagnosis in the series ranges from 15-455 days (mean of 55 days) and majority presented with advanced liver disease. It is obvious that severe cases, that present early to neonatal units, have not been included in this series. The Lucknow series is a retrospective analysis of 24 babies diagnosed as galactosemia, and who were well at discharge. The only two deaths alluded to were babies who were 'non-compliant' to therapy, and who were readmitted in the follow up period. This suggests a very optimistic outcome in treated cases, despite advanced liver disease and severe infections. Though patient data was collected over 11 years , the mean follow-up period of the survivors was only 30 months (range 6 – 78 months), and thus, inferences about long-term complications (as described in Western literature) [4,5], cannot really be made on the basis of this study.

The diagnostic tests for classic galactosemia are either detection of elevated erythrocyte galactose-1-phosphate concentration (difficult to estimate in India), or absent or barely detectable GALT enzyme activity (available now at many centers in the country). Assessment of urinary non-glucose reducing substances has been commonly used as a test for galactosemia, but this is only a screening test with significant number of false positive and negative results. Identification of bi-allelic mutations in the *GALT* gene, though still a research modality, can also be used as a diagnostic test for galactosemia. The GALT mutational profile in India appears to differ significantly from other populations studied, with N314D being the most common mutation with a frequency of 40% followed by Q188R at 2.7% [7]. Prenatal testing can be offered either by assessing GALT enzyme activity or molecular genetic testing (if disease-causing GALT mutations in the family are known). Molecular genetic testing is preferred over enzyme analysis.

Newborn screening for galactosemia has been a 'success' story in the west [6]. In the US, it is estimated that more than 80 babies with classic galactosemia are now identified at birth through the newborn screening programs, and for most of these infants, the potentially lethal sequelae of the disease are prevented by early intervention [6]. However, universal screening for galactosemia is not yet a 'reality' in our country, nor is it a priority [12], and as such, only increased awareness of the condition and a high index of suspicion can lead to early diagnosis and appropriate treatment.

The most important part of management of classic galactosemia is elimination of all galactose from the diet as soon as diagnosis is suspected [3,4]. This is one of the few conditions in which breast feeds must be stopped immediately, as also animal milk, and replaced by either calcium enriched soyamilk or lactose-free casein hydrolysates. Dietary treatment must be continued lifelong. In older children, complete elimination of galactose becomes difficult as many foods such as fruits, vegetables, breads and legumes contain significant amounts of galactose [3,4]. Moreover many recent studies have shown that such strict elimination may not even be desirable [2-4] though animal milk in any form must always be restricted. Infact, the major source of galactose even in well-controlled patients appears to be 'endogenous' production, and aim of future improved therapies would be to conceive of drugs to reduce endogenous production of galacose-1-phosphate, manipulate the metabolic pathways or stabilize the affected proteins [13].

Funding: None; *Competing interest*: None stated.

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