EDITORIAL

Galactosemia – A Not to be Missed Inborn Error of Metabolism

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The incidence of classical galactosemia in different countries has been reported to vary from 1 in 30,000 to 1 in 75,000 [1]. The exact population incidence in India is not known as there are no large studies available amongst low-risk population. In a recent study from Uttar Pradesh [2] about 13,500 newborns were screened, but no true positive case of galactosemia was detected. In another study from Andhra Pradesh [3], 10,300 babies were screened for Galactosemia; no case of galactose-1-phosphate uridyl transferase (GALT) deficiency was detected. This was probably due to small number of cases screened. If we extrapolate the reported incidence from the western world (1:30,000), about 87 babies every year are born with galactosemia in India. The prevalence of galactosemia in Indian children with suspected metabolic liver disease (MLD) has been reported to be about 20% [4], next to Wilson's disease and glycogen storage disorders. In our own unpublished data, high-risk (clinical suspicion, positive family history, *etc*) screening for galactosemia revealed prevalence of GALT deficiency as 12%.

The screening tests for galactosemia include a positive non-glucose sugar in urine (tested by Benedict's test or chromatography), with a negative glucostix test and measurement of Galactose-1-phosphate. Screening by urine reducing substances alone is not recommended as there is possibility of the test being false positive and false negative [5]. Erythrocyte GALT enzyme estimation is diagnostic of galactosemia. Galactosemia is classified as classical and clinical variant depending upon the level of GALT enzyme activity which is barely detectable in the former and about 1-10% in the latter. Although initial clinical features in either of them are similar, the long-term complications, including premature ovarian failure, are uncommon in clinical variant galactosemia. *GALT* gene mutation testing is advisable if available, and essential if prenatal diagnosis is to be planned. A definite genotype-phenotype correlation has been described and can be helpful in guiding prognosis [6]. A recent study from Northern India [7] highlighted the heterogeneity of mutations and importance of *GALT* gene analysis in the diagnosis of galactosemia in Indian patients. The same study also revealed that the mutational profile amongst Indians differs significantly from other populations.

There are varied views regarding inclusion of galactosemia in universal newborn screening programs as the outcomes have not been found to differ much in newborns diagnosed on newborn screening *versus* those detected early due to clinical suspicion and treated [8]. Even amongst siblings who were diagnosed and treated earlier, outcomes were similar [9].

Galactosemia is one of the rewarding inborn errors of metabolism (IEM) to treat. Special diets are easily available in India and are relatively much cheaper compared to diets for other metabolic liver diseases or IEMs amenable to special dietary therapy. In the present issue of *Indian Pediatrics,* Sen Sarma, *et al.* [10] from a pediatric gastroenterology setting of a tertiary care hospital have reported their retrospective experience of 24 (2% of all neonatal cholestasis cases) cases of galactosemia seen over 12 years. The clinical/laboratory profile, follow-up and predictors of outcomes have been discussed. The median (range) age of onset of symptoms and age at diagnosis /dietary intervention was 10 (3-75) days and 55 (15-455) days, respectively indicating delay in diagnosis. Of the 14 liver biopsies done 12 showed cirrhosis or bridging fibrosis. Out of 18 patients who were compliant with the diet, 87% cases survived. Follow-up for at least 6 months or more was available in 18 patients and all showed normalization of liver transaminases within a median time of about 6 months. Language delay in 6, fine motor problems and hyperactivity in one each was reported in 13 cases evaluated. Improvement in liver function was not influenced by high pediatric end-stage liver disease (PELD) scores but was significantly quicker in patients diagnosed before 4 weeks.

Available literature suggests that early diagnosis and treatment with lactose-free diet in initial 1-2 weeks of life reduces complications of liver failure and mortality.

However, most follow-up studies in patients with classical galactosemia suggest that despite adequate treatment from an early age, there is risk of cognitive, motor and speech problems. Additionally, almost all females with classic galactosemia manifest later in life with premature ovarian failure causing hypergonadotropic hypogonadism [11]. Developmental delay and speech problems have been described in about 50% of cases while motor function is reported to be impaired in about 18%. About 80% of girls have premature ovarian failure. Prediction of outcomes have been reported to be based on the level of erythrocyte GALT activity, genotype, compliance with therapy and age at which good therapeutic control was achieved.

The study by Sen Sarma, *et al.* [10] emphasizes need for early diagnosis and good response to dietary intervention even in severely affected cases. Small numbers, retrospective data and short-term follow up are the major limitations. None the less, there is a clear message for high index of suspicion, importance of early diagnosis and dietary compliance. This applies to many other easily and economically treatable IEMs.

Lactose-restricted diet is the presently recommended therapy for classical and clinical variant galactosemia. A very strict control is desired with no galactose in diet, more so in the initial stages. Any baby with clinically suspected galactosemia, should be initiated on soy-based diet till the time enzyme report is available. After the neonatal period, a strict lactose-free diet is controversial. Despite strict dietary control and early diagnosis, long-term complications are common as discussed above. The reason for long-term complications like neurodevelopmental impairment and hypogonadism is probably the endogenous synthesis of galactose or from abnormal galactosylation [12]. Newer therapeutic strategies targeted at controlling galactose 1-phosphate production should be worked on aggressively [11]. As inhibition of Galactokinase (GALK) is likely to prevent the accumulation of galactose-1-phosphate (which is probably the most toxic metabolite) from diet and endogenous sources, efforts towards making a therapeutic agent as small molecule GALK inhibitor seems promising. Some work in this direction has been initiated [13,14].

Meanwhile as we await better therapies, pediatricians should focus on early detection by keeping a high index of suspicion, early dietary intervention, ensuring dietary compliance, regular follow-up and early intervention for long-term complications.

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