Galactosemia: Clinical Manifestations, Diagnosis and Outcome of Early Management

Objectives of study: To see variable clinical manifestations of patients with galactosemia, accuracy of screening test employed at our centre, its relation to specific enzyme analysis and outcome of these patients in regards to early removal of galactose from diet.

Duration of study: 20/04/2012 – 14/08/2014 two years and four months.

Place of study: Department Of Pediatric Gastroenterology Hepatology at The Children's Hospital and Institute of Child Health. Lahore

Material and Methods: It was a prospective, observational study. A total number of 22 patients diagnosed with galactosemia were included. Urine for reducing substance (Benedict Test) and dipstick for glucosuria was done. Diagnosis was confirmed by enzyme analysis GAL-1-PUT assay.

Results: Patients had mean age 112 days with a range from 8 - 510 days out of these 14 (63.6%) were male while 8 (36.4%) were females. All patients had low GAL -1-PUT activity. Serum bilirubin Mean = 9.2193, range 0.20 – 34 mg/dl serum ALT Mean= 159.60, range 19 – 654, Serum GGT Mean=17.6667, range 12 – 22. Cataract was seen in 3(13.6%), central nervous manifestations was observed in 3 (13.6%), hepatomegaly was present in 22 (100%), splenomegaly was present in only 5(22.7%), ascites in 16(72.7%), hemolysis in 6(27.2%), sepsis in 13 (59%) blood culture grew E. coli in 8(36.3%) staphylococcus aureus in 1 (4.5%). Urine for reducing sugars was positive in 21(95.4%) while dip stick was negative in all. All patients improved after institution of galactose free diet and supportive care. Infections were treated with antibiotics and patient improved and discharged within mean time of 10 days. Jaundice, visceromegaly, liver enzymes were normalized in mean time of one month period in all patients.

Conclusion: Common mode of presentation of galactosemia was with jaundice, hepatomegaly, ascites, hyperbilirubinemia, hypertransaminasemia and sepsis. Urine for reducing substances combined with Dipstick for glucosuria is highly effective test for the diagnosis of Galactosemia and results closely correlate with GAL-1-PUT assay. The outcome of properly treated children seems to be good and showed rapid improvements in symptoms and signs after restriction of galactose.

Key words: Galactosemia, Sepsis, GAL-1-PUT.

Introduction

The clinical manifestations of these disorders are often non-specific and easily confused with other common disorder. This often results in misdiagnosis with a delay in starting treatment.

Rarity of these disorders is another important reason for delay in diagnosis as a high index of suspicion is required to reach at an early and correct diagnosis.

Galactosemia is a rare genetic, metabolic disorder with estimated prevalence between 1
in 30,000-60,000 live births. The defect is deficiency of the enzyme Galactose 1 phosphate Uridyl transferase (GAL-1-PUT).  

Galactosemia has an Autosomal recessive mode of inheritance that leads to a deficiency in the enzyme GAL-1-PUT which is essential for galactose metabolism.

There is a strong correlation between untreated galactosemia and E. coli sepsis in neonates. Another frequent finding in untreated galactosemia patients is cataract. The disease was first described in Germany by Friedrich Goppert (1870-1927) in early 20th century. The causative defective gene was detected by Herman Kalckar in 1956. The disease is suspected on clinical grounds such as the manifestations of liver disease. Diagnosis is greatly aided by the screening tests (clinitest in urines, galactose-1-phosphate in erythrocytes). Definitive diagnosis is established by demonstrating low levels of enzyme GAL-1-PUT in erythrocytes. We aimed to study the different clinical features, laboratory parameters, role of screening test for diagnosis of galactosemia and outcome of early recognition and prompt removal of galactose from diet.

**Materials and Methods**

This is a prospective, observational study conducted at the Department of Pediatric Gastroenterology- Hepatology, The Children's Hospital & the Institute of Child Health, Lahore over a period of 2 years and 4 months i-e from 20/04/2012 till 14/08/2014. All patients who were diagnosed as Galactosemia were included in the study. Informed consent was taken from all patients’ parents/guardian. At presentation, age and presence or absence of jaundice and hepatosplenomegaly was noted clinically. 3cc coagulated venous blood was sent to hospital laboratory for analysis of serum bilirubin, ALT, GGT and albumin. 2.5ml citrated venous blood was sent for PT, APTT quantification. Blood culture was also done for each patient. Eye examination for cataract was done by a consultant ophthalmologist. Urine for reducing substances (Benedict test) was done in each patient while on milk. Simultaneously, Dip stick for glycosuria was done in the same sample. Positive urine reducing substances with negative dip stick was considered suggestive of galactosemia. The Diagnosis was confirmed on the basis of enzyme analysis GAL-1-PUT assay. The sample was transported as dried blood spot on a filter paper to India for GAL-1-PUT assay. Data analysis was done using SPSS version 19.

**Results**

Mean age of these patients was 112 days with a range from 8 - 510 days out of these 14 (63.6%) were male while 8 (36.4%) were females. GAL -1-PUT assay was positive in all patients, serum bilirubin Mean = 9.2193, range 0.20 – 34 mg/dl serum ALT Mean= 159.60, range 19 – 654, Serum GGT Mean=17.6667, range 12 – 22. Cataract was seen in 3(13.6%), central nervous manifestations was observed in 3 (13.6%), hepatomegaly was in 22 (100%), splenomegaly was present in 5(22.7%), ascites in 16(72.7%), hemolysis in 6(27.2%), sepsis in 13 (59%) E. coli was cultured from blood in 8(36.3%) and 1 (4.5%) patient grew staphylococcus aureus. Screening test of urine for reducing sugars was done in all patients and it was positive in 21(95.4%) while dip stick was negative in all. Lactose free milk was started to all patients and they were put on regular follow-up. Symptoms gradually
improved after institution of galactose free diet. Infections were treated with antibiotics and patient improved and discharged within mean time of 10 days. Jaundice, visceromegaly, liver enzymes were normalized in mean time of one month period in all patients.

Table I: Presenting Features of Galactosemia Patients

<table>
<thead>
<tr>
<th>Features</th>
<th>No of Patients</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenomegaly</td>
<td>5</td>
<td>22.7</td>
</tr>
<tr>
<td>Ascites</td>
<td>16</td>
<td>72.7</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>6</td>
<td>27.2</td>
</tr>
<tr>
<td>Sepsis</td>
<td>13</td>
<td>59</td>
</tr>
<tr>
<td>Blood culture Positive</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>E.coli</td>
<td>8</td>
<td>36.3</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Urine for reducing sugars Positive</td>
<td>21</td>
<td>95.4</td>
</tr>
</tbody>
</table>

Table II: Gal-1-put levels and Liver functions in Galactosemia Patients

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gal-1-Put</td>
<td>0.4205</td>
<td>0.06 – 0.92</td>
</tr>
<tr>
<td>Serum Bilirubin</td>
<td>9.2193</td>
<td>0.20 – 34</td>
</tr>
<tr>
<td>Serum ALT</td>
<td>159.60</td>
<td>19 – 654</td>
</tr>
<tr>
<td>Serum GGT</td>
<td>17.67</td>
<td>12 – 22</td>
</tr>
</tbody>
</table>

Discussion

True incidence of galactosemia in our country is not known but owing to inter - cast and cousin marriages, in our community, makes it ‘a relatively common’ disorder.
Galactosemia is a metabolic disease caused by the deficiency of enzyme GAL-1-PUT which is the enzyme responsible for the key step in galactose metabolism.
This study is in continuation with the study done from our department and published in 2004. In which Diagnosis of galactosemia was made in 18 infants over the study period. Their age at presentation ranged from 35 days – 9 months (median 2 ½ months). There were 12 males and 6 females (M: F ratio 2:1). Most common mode of presentation was fulminant hepatic failure (FHF). Although cataracts were present in the majority of patients, they were not the reason for referral. Laboratory values showed raised bilirubin and universal coagulopathy. Fourteen patients responded to galactose elimination and showed dramatic improvement in Clinical and laboratory parameters. Four patients (22 %) died due to FHF. 12
Patients with galactosemia have variable presentation. Common presentations are vomiting, diarrhea, jaundice and poor weight gain. Symptoms typically start after the ingestion of galactose containing foods; i.e. breast milk or cow’s milk based formulas. 7
A study published in journal of inherited metabolic disorder shows that most common findings are 9: Presence of Jaundice (74%), Vomiting (47%), Hepatomegaly (43 %), Failure to thrive (29 %), Poor feeding (23%), Lethargy (16%), Diarrhea (12 %) and Sepsis (10 %). Among infants with sepsis, the most common organism is Escherichia coli sepsis (36.3%) while less frequent findings are coagulopathy, ascites, and seizures.
In our study jaundice was seen in 66.6%, hepatomegaly in 100%, ascites in 72.7% and sepsis in 59% while E.coli was isolated in 61.5% of septic patients.
The importance of screening test i-e presence of reducing substance in urine in the absence of glycosuria as determined by dipstick (Clinitix test), along with other signs and symptoms of galactosemia is highly suggestive of this disorder and perhaps can be used with high degree of certainty in countries where
metabolic laboratories are not available to confirm specific enzyme deficiency like in our country.

This Screening test in our study was positive in 21 out of 22 i-e 95.4% of enzyme deficient proven cases of galactosemia. Previous study from our department which was published in 2004 also highlights the importance of this screening test as very specific test for screening patients suspected of galactosemia. 

Lactose in milk is split into glucose and galactose. Because of a blockade in the metabolic path of galactose, it is excreted in urine and is detected as reducing substance by Fehling’s or Benedict’s reagent and concomitantly test for glucose performed by glucose oxidase test strip is negative. In our study we diagnosed sepsis in 13 (59%) out of 22 subjects out of these E Coli was isolated in 8 (61.5%). We also isolated a staphylococcus aureus in one of our patient. Galactosemia predisposed to E coli sepsis in early life. E. coli sepsis is considered to be an important indicator of morbidity and mortality in patients with galactosemia. most important cause of death in infants with galactosemia is sepsis. high galactose levels is considered to depress neutrophil function either directly or by means of a metabolite resulting in high risk for sepsis especially in neonates. Commonest organism causing sepsis in these patients is E Coli, followed by Klebsiella, Staphylococcus, Beta hemolytic Streptococcus and Streptococcus faecalis. Another important indicator of outcome is the time of diagnosis. Early diagnosis and prompt withdrawal of galactose containing diets is the most important measure needed for good prognosis. Important challenge lies in the fact that there is a wide variability of clinical presentation and not all patients present with typical acute manifestations.

Diagnosis of galactosemia is confirmed by demonstration of low GAL-1-PUT activity in the erythrocytes and it is the time tested diagnostic gold standard. Demonstration of high levels of galactose and galactitol in urine by gas chromatography is also diagnostic. Main stay or galactosemia therapeutics is complete exclusion of galactose from diet; and it has to be done best as soon a diagnosis is suspected. However once the patient is on galactose exclusion diet, urine testing for reducing substances or gas chromatography is rendered ineffective; thereby, leaving GAL-1-PUT assay as the only valid possible confirmatory test.

Early diagnosis of Galactosemia needs a high index of suspicion. Sick neonates and infants with sepsis, jaundice, early ascites and features of hepatic failure like hypoglycemia, hypoalbuminemia and coagulopathy are strong candidates for galactosemia screening. The most convenient and cost effective approach towards diagnosis of galactosemia is to screen by means of urinary reducing substances with later confirmation of diagnosis by the GAL-1-PUT assay. Many developed countries are screening all newborns for galactosemia; thus greatly helping in early diagnosis.

Considering the need for timely diagnosis; there is an urgent requirement for a Central Facility for metabolic testing in our country. Early diagnosis is imperative in preventing irreversible liver disease. Long term outcome also depends upon the particular genetic mutations in addition to strict dietary compliance.

These subjects included in our study are being followed up carefully to see the incidence of
mental retardation and other neurological sequelae.

**Conclusion**

Common mode of presentation of galactosemia was with jaundice, hepatomegaly, ascites, hyperbilirubinemia, hypertransaminasemia and sepsis. Urine reducing and Dipstick for glycosuria combined is a highly effective test for galactosemia and results closely correlate with GAL-1-PUT assay. The outcome of properly treated children seems to be good and showed rapid improvements in symptoms and signs after restriction of galactose. Though mass screening is still not available in Pakistan for Galactosemia, early detection and early institution of therapy is possible with effective screening test.

**References**

2. Galactosemia the University of Utah, Genetics Science Learning Center. 2008.