RESEARCH PAPER

Classical Galactosemia Among Indian Children: Presentation and Outcome from a Pediatric Gastroenterology Center

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Objective: To analyze the presentation and predictors of outcome of children with galactosemia.

Methods: Analysis of clinical, laboratory, microbiological profile and outcome of patients fulfilling the diagnostic criteria: i) clinical setting; ii) reduced erythrocyte Gal-1-PUT enzyme activity; and iii) unequivocal response to lactose-free diet.

Results: 24 patients; median age of symptom onset and diagnosis: 10 (3-75) d and 55 (15-455) days, respectively. 71% had uncorrectable coagulopathy; 71% systemic infections; and 54% had ascites. Outcome: consisted of 87.5% survival with normalization of liver function tests at 5.5 (1-24) months follow-up.

Conclusion: Despite delayed referral, high Pediatric end-stage liver disease scores and systemic infections, long-term outcome in galactosemia is rewarding. A subset of children have developmental delay.

Keywords:*Galactose, lactose-free diet, Outcome*.

Classical galactosemia is an autosomal recessive disorder of galactose metabolism occuring due to deficiency of the enzyme galactose-l-phosphate uridyl transferase (Gal-1-PUT), and responding to a galactose restricted diet [1]. In the absence of this enzyme, galactose is converted into toxic by-products (galactitol, galactose-1-phosphate and galactonate) that affect the liver, brain, kidneys, lens and gonads. There is scarcity of data on clinical profile and natural history among Indian children, resulting in lack of awareness of this potentially treatable condition. We studied the presentation and predictors of outcome of children diagnosed to have galactosemia.

METHODS

We analyzed the data of children with confirmed galactosemia from July, 2003 to June, 2014 admitted in the Pediatric Gastroenterology department of our Institution, a large referral hospital in Northern India. Enrolled patients fulfilled all three diagnostic criteria: (*i*) clinical features suggestive of galactosemia, (*ii*) reduced or undetectable erythrocyte Gal-1-PUT enzyme activity, and (*iii*) unequivocal response to lactose-free diet. We retrieved the clinical, laboratory features and follow-up data from hospital electronic records. We traced majority of our patients telephonically for a fresh visit to document the current status at the time of analysis. At admission, all children underwent routine blood tests and screening for sepsis. Neutrophilia and leucocytosis were interpreted as per the age-related cut-offs (maximum limit of range) [2]. Diagnostic paracentesis was done in all patients with ascites. Presence of cataract was confirmed by the ophthalmologist with direct ophthalmoscopy. While on lactose containing diet at admission, three samples of urine were tested for presence of non-glucose reducing substances by Benedict's test (glycosuria ruled out by urine dipstick method). Gal-1-PUT assay was done by spectrofluorometry (quantitative Beutler test) [3]. Normal values of Gal-1-PUT varied between 20-50 U/gHb. Levels ≤10 U/gHb are considered confirmatory of galactosemia. Values <5 U/gHb (lowest laboratory limit) were reported undetectable. The test was reconfirmed after 12 weeks of initial presentation in children who had earlier received packed red cell transfusion or had presented with hemolysis. Percutaneous liver biopsy was done at admission in all patients in whom the coagulopathy corrected and ascites resolved. Additionally, upper gastrointestinal endoscopy was performed as indicated. Pediatric end-stage liver disease (PELD) scores were calculated as per standard formula and scores of 17 and 25 were taken as cut-offs for comparison of various parameters [4,5]. Systemic infection was defined as any one or more of the following: (*a*) bacterial or fungal culture

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positivity of blood and/or urine, (*b*) pneumonia on chest X-ray, (*c*) cerebrospinal fluid analysis suggestive of pyogenic meningitis, (*d*) spontaneous bacterial peritonitis (SBP) or culture negative neutrocytic ascites (CNNA). SBP was defined as absolute neutrophil count ≥250 cells/mm^3 and ascitic fluid culture positivity. CNNA was defined as absolute neutrophil count ≥250 cells/mm^3 with sterile ascitic fluid culture [6]. Presumed infection in a sick child was defined as high clinical suspicion with neutrophilic leukocytosis with (out) thrombocytopenia (platelet count <100,000/mm^3) with (out) positive semi-quantitative C-reactive protein (>6 mg/dL) but sterile body fluid cultures.

All patients were counseled and discharged on lactose-free diet and supplements. Patients were thereafter periodically followed up. Patients with at least 6 months of follow-up were analyzed for outcome. Compliance to lactose-free diet, clinical improvement, and time taken for normalization of liver function tests were assessed. Normal liver function tests was defined as normal albumin, international normalized ratio (INR) and transaminases <2 times upper limit of normal. Surgery was advised by the ophthalmologist if the cataract status was dense, persisted despite diet-compliance or if the child was at risk of amblyopia at 1-3 months of follow-up. Children older than 18 months of age were subjectively assessed for development in all domains.

Statistical analysis: For comparison between two groups, we used chi-square test for categorical variables. The clinical and laboratory factors associated with outcome were analyzed by a logistic regression analysis. SPSS version 16.0 (SPSS Inc, Chicago, IL, USA) was used for all statistical analysis, and a *P* value of <0.05 was taken as significant.

RESULTS

Out of 1189 neonatal cholestasis patients, 24 children (16 boys) were diagnosed to have galactosemia. Overall median age of onset of symptoms and age at diagnosis (age at dietary intervention) was 10 (3-75) d and 55 (15-455) d, respectively. There was a median delay in diagnosis of 45 (12-380) d. All had history of neonatal jaundice. Majority had uncorrectable coagulopathy and ascites (***Table* I**).

Liver function tests profile (median with range) showed total/direct bilirubin: 10.8 (2.8-24)/5.0(1.6-12.0) mg/dL, aspartate/ alanine aminotransferase: 191 (52-861)/84(26-525) U/L; serum albumin: 2.7 (1.9-4.2) g/dL; alkaline phosphatase: 937(143-1464) U/L; gamma-glutamyl transpeptidase: 24 (8-818) (U/L), and international normalized ratio (after vitamin K): 1.7 (1.0-6.8). Positive urinary non-glucose reducing substance samples (≥2 of 3) were seen in 22 cases. Only two children had Gal-1-PUT levels of 8.7 and 10 U/gHb; rest 22 had undetectable levels. Twelve of 14 liver biopsies done showed cirrhosis or bridging fibrosis; 2 had macrovesicular steatosis. Median (range) PELD score at diagnosis was 24 (9-51).

TABLE I CLINICAL PROFILE OF PATIENTS WITH GALACTOSEMIA AT ADMISSION (*N*=24)

Clinical profile	*n* (%)
Symptoms[$]	
Poor feeding	16 (67)
Lethargy	15 (53)
Generalized tonic clonic seizures	7 (29)
Signs	
Splenomegaly	24(100)
Ascites	13 (54)
Bilateral cataract	13 (54)
Other features	
Uncorrectable coagulopathy[*]	17 (71)
Recurrent hypoglycemia	15 (63)
Transient hemolysis[#]	4 (16)
Sibling deaths	9 (38)
Consanguinity	3 (13)

[$]Jaundice and hepatomegaly present in all children, [*]International normalized ratio (after vitamin K injection) > 1.5, [#]Hemoglobin level below age specific cut-off [2], reticulocyte count >2% and peripheral smear suggestive of hemolysis.

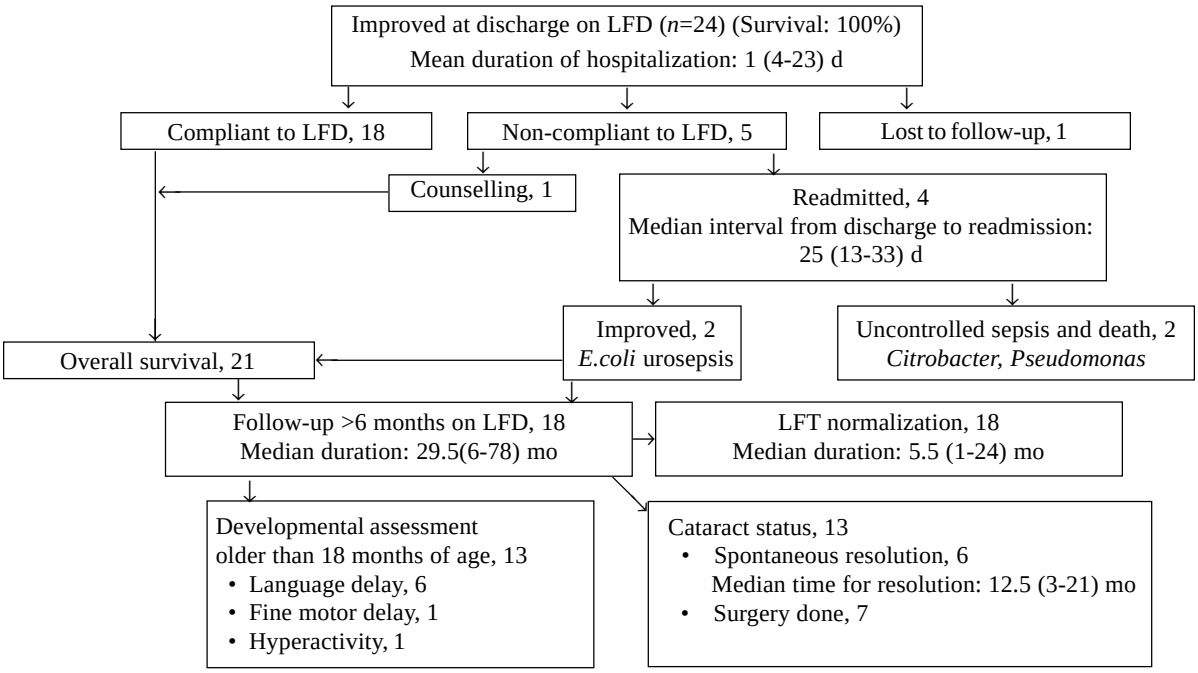
***Table* II** shows the composite infectious profile of all infected patients. 13 children with systemic infection had a definitive infective focus at admission. Additionally 4 infants initially stable were readmitted with systemic infection at follow-up as they were non-compliant to LFD. 11/17 (68%) systemic infection had a gram negative infection, mostly with *Escherichia coli* (*n*=8). Symptom onset <2 weeks of age (*n*=5) was significantly associated with systemic infection (*P*=0.002) than those with >2 weeks (*n*=8). PELD ≥25 at first admission was significantly associated with systemic infection (*P*=0.04, OR 7.0, 95% CI 1.04-46.9).

***Fig.* 1** shows the natural history of galactosemia patients on follow-up. Mean days of hospitalization was 12 (4-23) d. Long term follow-up (≥6 months) was available in 18 patients who had good LFD compliance and were analyzed for outcome. LFT improved in 4.5 (1-18) and 15 (4-24) mo in those diagnosed <4 weeks (*n*=12) and >4 weeks (*n*=6) of age, respectively (*P*=0.02). No difference in LFT normalization was seen with PELD cut-off scores of 17 or 25.

TABLE II PROFILE OF INFECTIONS FIRST AT ADMISSION AND READMISSION IN NON-COMPLIANT PATIENTS

*Type of infection**	*n* (%)	*Details*
Systemic infection[#]	17 (71)	
Blood culture positive*	9 (38)	*E.coli* (*n*=3), CONS (*n*=2), *Klebsiella* (*n*=1), *Pseudomonas* (*n*=1), *Citrobacter* (*n*=1), Methicillin-resistant *S. aureas* (*n*=1)
Urine culture positive*	7 (29)	*E.coli* (*n*=4), Candida (*n*=3)
Respiratory infection	1 (4)	Lobar pneumonia on chest *X*-Ray (left upper lobe)
Pyogenic meningitis	1 (4)	CSF culture negative
SBP or CNNA	3 (12.5)	*E.coli* (*n*=1), ascitic fluid culture negative (*n*=2)
Presumed infection	4 (17)	Not applicable

*[#]Multiple site infections :Blood and urine culture positive (3); blood culture positive and CNNA (1); CNNA and meningitis (1); blood culture positive and lobar pneumonia (1). *4 readmitted non-compliant patients had Pseudomonas and Citrobacter in blood culture (1 each) and E.coli in urine culture (2); CNNA: Culture-negative neutrocytic ascites; SBP: spontaneous bacterial peritonitis.*



LFD: lactose-free diet; E.coli: Escherichia coli; LFT: liver function tests

Fig. 1 *Clinical course and outcome of galactosemia patients.*

One child operated at 8 months was permanently blind due to irreversible amblyopia. Thirteen children older than 18 months age were assessed for development. Of 6 with initial language delay, two showed catch-up at subsequent follow-up. Hypodensities in white matter on imaging with persistent fine motor delay at 24 months was noted in one child.

DISCUSSION

This composite study reported the presentation, natural history and predictors of outcome in galactosemia among Indian children. Though the exact Indian prevalence is not known, galactosemia constituted 2% of all our neonatal cholestasis referrals. In an analysis of 1008 cases of neonatal cholestasis, galactosemia constituted 4% of all cases and 35% in the metabolic liver disease sub-group [7]. Our median age of diagnosis was comparable to that reported by Singh, *et al.* [8]. Delay in diagnosis resulted in higher hepatocellular dysfunction (100% *vs.* 64-89%), systemic infection (71% *vs.* 13-40%), cataract (54% *vs.* 13-30%) and seizures (29% *vs.* 3-17%) in our study compared to other series where early

WHAT THIS STUDY ADDS?

- There is a considerable delay in referral of galactosemia patients in India.
- Good clinical outcome is seen despite high PELD scores and systemic infections at presentation.

referral was attributable to neonatal screening [9,10]. In the study by Honeyman, *et al*. [10], 95% neonates were started on LFD by day 30 of life .

E.coli culture positivity was higher in our series (47% *vs*. 24%) compared to Waggoner, *et al*. [9]. Transplecental deficiency of IgM bactericidal opsonic antibodies-complement system in neonates and inhibition of leucocyte bactericidal activity by accumulated galactose predispose to gram-negative infections [11,12].

The disease has a favorable prognosis by timely referral, introduction of LFD, and long term compliance; Reintroduction of lactose in such cases may be fatal [13]. LFT improved by median interval of 5.5(1-24) months of starting therapy, significantly earlier in those diagnosed <4 weeks. PELD cut-off's >17 (United Network for Organ Sharing Status for liver transplant) and >25 (high incidence of death rate: 4.6/1000 patient-years) did not influence the improvement in LFT at follow-up [3,4]. Spontaneous resolution of cataract was not related to age at diagnosis or dietary intervention. This is in contrast to Waggoner, *et al*. [9] who showed that 90% cataracts resolve spontaneously if dietary intervention is begun at mean of 77 days of age [9]. Given the risk of irreversible ambylopia, early cataract surgery (1-8 weeks of life) is presently recommended by most pediatric ophthalmologists as performed in seven of our cases who continued to have dense cataract despite four weeks of LFD [14].

Bosch, *et al*. [15] found subnormal cognitive outcomes in galactosemia children older than six years age, despite strict adherence to diet [15]. Small number of patients and retrospective design were the main limitations of our study. As a result, we could not assess IQ, use development scoring systems or identify risk factors for delayed milestones.

A cholestatic neonate with ascites, coagulopathy, seizures, family history of sibling death, consanguinity and/or hemolysis should raise a suspicion for galactosemia. Despite high PELD scores (advanced disease) and systemic infections, this condition is salvageable with lactose-free diet. Neonatal screening or early diagnosis are helpful strategies to having a favorable outcome.

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