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Early diagnosis of classic galactosemia in the first week of life: A case series and implications for national newborn screening policy

Mahli Batuhan Ozdogar[1], Dilem Eris[1], Muzaffer Coskun[1], Ozgur Olukman[2]

[1]Specialist in Pediatrics, Çiğli Training and Research Hospital, Department of Pediatrics, İzmir, Türkiye
[2]İzmir Bakircay University, Faculty of Medicine, Department of Pediatrics, Division of Neonatology, İzmir, Türkiye

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Abstract

Classic galactosemia is an autosomal recessive metabolic disorder with an estimated incidence of 1 in 24,000 in countries where consanguinity is common. Due to its nonspecific clinical presentation, early diagnosis during the neonatal period remains a challenge. Delayed diagnosis is associated with high morbidity and mortality. This study aims to present seven cases diagnosed within the first week of life, to emphasize the impact of early diagnosis on clinical outcomes, and to underscore the need to include galactosemia in the national newborn screening (NBS) program. Seven newborns diagnosed with classic galactosemia during the first postnatal week were retrospectively evaluated. Clinical, demographic, laboratory and genetic findings were reviewed. Among the seven patients (3 males, 4 females), the earliest diagnosis was made on postnatal day 1 and the latest on day 6. Consanguinity (first-degree cousin marriage) was identified in four cases. Initial symptoms were nonspecific, including feeding difficulties and lethargy. Physical examination revealed hypotonia, jaundice, hepatomegaly, signs of sepsis, and seizures. Laboratory investigations showed elevated liver enzymes, direct hyperbilirubinemia, prolonged coagulation tests, hypoglycemia, thrombocytopenia, and positive urinary-reducing substances (URS). The diagnosis was confirmed by demonstrating absent or markedly reduced galactose-1-phosphate uridyltransferase (GALT) enzyme activity and genetic testing, as well. Except for one asymptomatic patient, all showed significant clinical and biochemical improvement within one week following the initiation of a lactose-free diet. Galactosemia is more prevalent in countries with high consanguinity rates and remains a critical but underdiagnosed health issue due to the lack of routine newborn screening. Our findings support the inclusion of galactosemia in the national newborn screening program. Early identification through screening or clinical suspicion can prevent potentially fatal complications and significantly improve prognosis with simple dietary intervention.

Keywords: Galactosemia, newborn screening, neonatal metabolic disorders, early diagnosis, GALT deficiency, lactose-free diet, consanguinity

Introduction

Galactosemia is an autosomal recessively inherited disorder of carbohydrate metabolism. Altered metabolism of galactose caused by deficient activity of one of three enzymes (galactose-1-phosphate uridyl transferase (GALT), galactokinase (GALK), uridine diphosphate (UDP), galactose 4-epimerase (GALE)) results either in elevated blood galactose or its toxic metabolites that ultimately lead to specific organ dysfunction [1,2]. Classic galactosemia, caused by a complete deficiency of GALT due to the mutations of the related gene located on chromosome 9p13, is the most common and severe type [3-5]. Classic galactosemia occurs in approximately 1 of 60.000 live births [3,5]. However, the reported incidence of galactosemia varies geographically from 1/30.000 to 40.000 in Europe [6] and to 1/1.000.000 in Japan [7]. Studies from Turkiye, where consanguineous marriages are frequent, report a higher incidence of 1/24.000 [8,9].

The enzyme GALT converts galactose-1-phosphate (galactose-1-P) to uridine diphosphate galactose (UDP-galactose). In the absence of GALT, this conversion cannot occur, and blood galactose-1-P concentration increases gradually accumulating and causing harm to the liver, kidneys, brain, tongue, lens and skin fibroblasts. Infants are asymptomatic at birth. However, since galactose is a sugar found primarily in human and bovine milk, newborns present with poor feeding, vomiting, dehydration,

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Corresponding Author: Mahli Batuhan Ozdogar, Specialist in Pediatrics, Çiğli Training and Research Hospital, Department of Pediatrics, İzmir, Türkiye
Email: ozdogarbatuhan@gmail.com

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failure to thrive, jaundice, lethargy, hypotonia, diarrhoea or sepsis after initiation of feedings with breast milk or cow's milk-based formula in the first few days of life [5,10]. While in the early neonatal period hepatosplenomegaly, liver failure, coagulopathy, renal tubular dysfunction and signs and symptoms of sepsis are prominent, neurological dysfunction and cataracts become apparent with the progression of the disease [11]. Most frequently Gram-negative bacteria, especially Escherichia coli (*E.coli*), are isolated from the blood cultures of infants with sepsis [12]. The early signs and symptoms like feeding intolerance, liver dysfunction, jaundice, bleeding disorder, failure to thrive, sepsis, and even cataracts can be prevented or improved by early diagnosis and treatment. However, infants can still have chronic and progressive neurologic impairment. Delayed diagnosis paves the way for undesirable short and long-term poor results [13].

Many countries include galactosemia in their newborn screening (NBS) programs. Although the reported incidence of the disease is 2,5 times higher than in other countries, the current NBS program does not include galactosemia in Turkiye. It is well known that affected infants may become symptomatic before the screening results become available [14]. Since the benefits of early diagnosis are clear, clinicians should be aware of the relevant signs and symptoms and consider the diagnosis before they get the test results. Despite prenatal diagnostic tools, counselling and carrier screening patients diagnosed in the first week of life are quite rare.

In this article, we present 7 newborn infants diagnosed early in the first week of life through the caution of clinicians. Thus, we want to emphasize the relationship between early diagnosis and favourable outcomes and the need to include the disease in the national NBS program in Turkiye.

Material and Methods

In this retrospective case study, we evaluated the files of 7 newborn infants diagnosed as having galactosemia and hospitalised at the neonatal intensive care unit (NICU) between January 2020 and December 2024. Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Izmir Bakircay University (Approval Number:2365, Date:14/08/2025). Written patient informed consent was received from patients' families. The inclusion and exclusion criteria were as follows: Newborns who were hospitalized in the NICU of İzmir Bakırçay University between January 1, 2020, and December 31, 2024, were eligible for inclusion in the study. Eligible infants had a confirmed diagnosis of classical galactosemia based on the measurement of GALT enzyme activity and/or genetic analysis. Only those diagnosed within the first seven days of life and whose complete clinical, laboratory, and genetic data were available in patient records were included. Newborns were excluded if the diagnosis of galactosemia was made after the first week of life, if GALT enzyme activity or genetic testing results were unavailable or questionable, if clinical, laboratory, or genetic data in patient files were incomplete or insufficient, or if written informed consent from the parents was missing.

Gender, gestational age, birth weight, initial symptoms at admission, physical examination findings, the time interval between admission and diagnosis, consanguinity between parents, and history of galactosemia in the family were recorded. Laboratory results including blood biochemistry (blood glucose, sodium, potassium, total and direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST)), coagulation tests (prothrombin time (PT), activated partial thromboplastin time (APTT)) and presence of urinary reducing substances (URS) were evaluated. Results of septic work-up including peripheral blood smear, C-reactive protein (CRP), procalcitonin (PCT) and haemoculture were recorded. A quantitative assay of red blood cell GALT activity (normal:>3.00 U/g Hb), using a fluoroimmunoassay, was used to confirm the diagnosis and identify variants with partial enzyme activity. Besides blood total galactose (normal:<10 mg/dL), free galactose (normal:<5 mg/dL) and galactose-1-P (normal:<5 mg/dL) levels were evaluated. DNA analysis and full gene sequencing were performed to define any mutation.

Statistical analysis was performed by using IBM Statistical Package for the Social Sciences 25.0 (SPSS Inc.; Chicago, IL, USA). Data were presented as mean±standard deviation or median (min/max).

Results

Between January 2020 and December 2024, 7 newborn infants were diagnosed with galactosemia and hospitalised in the NICU with various presentations. While 3 infants (42.9%) were male, 4 (57.1%) were female. The median birth weight was 3300 (min/max: 2980/3735) grams and the median gestational age was 38+1 weeks (min/max:37+1/39+3). The earliest diagnosis was made on the first day of life and the latest was made on postnatal day 6. The infant diagnosed on the first day of life was an asymptomatic infant who was diagnosed before initiating breastfeeding because of the history of galactosemia in his sibling. We demonstrated both the absence of GALT activity and the presence of Q188R missense mutation in all of the patients. Four infants had a history of first-degree cousin marriage between the parents. The most common initial symptoms were Jaundice, poor feeding, vomiting, and lethargy. On physical examination 6 infants appeared jaundiced, 4 infants had marked hypotonia and diminished newborn reflexes, and 1 infant had hepatomegaly. One infant was admitted to NICU with seizures and encephalopathy on postnatal day 7 whose blood glucose measurement was 31 mg/dL. Blood culture-proven late-onset neonatal sepsis due to *E.coli* was demonstrated in another infant who was hospitalised on postnatal day 4. Laboratory examination revealed elevated transaminases, prolonged coagulation tests and direct hyperbilirubinemia in 6 patients, presence of URS in 5 patients, hypoglycemia in 2 infants, thrombocytopenia, elevated CRP and PCT in 1 septic patient. The diagnosis was confirmed by demonstrating elevated total blood galactose, free galactose and galactose-1-P levels as well as absent or decreased GALT activity. On DNA analysis, all patients had Q188R mutation.

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An asymptomatic patient who was diagnosed because of sibling history was never breastfed. All infants received lactose-free infant formula initially which was replaced with soy-based infant formula after consultation with a dietician and a pediatric specialist in inborn errors of metabolism. Clinical symptoms diminished and laboratory results improved in 10-14 days after appropriate dietary intervention. The summary of the clinical and laboratory findings of infants is shown in Table 1.

Table 1. Clinical and laboratory findings of infants with classic galactosemia

Patient/ Gender	Postnatal age at diagnosis	Sign/ symptom	Physical Exam	AST (IU/L)	ALT (IU/L)	TB/ DB (mg/dL)	Blood glucose (fasting) (mg/dL)	PT (sec)	aPTT (sec)	URS	Sepsis, elevated CRP	GALT activity/ gene mutation
1/ F	4	Jaundice, vomiting	Hypotonia, icterus, hepatomegaly	130	280	18/5.6	71	27	92	+	+ (*E.coli*)	Absent/ Q188R
2/ F	6	Jaundice, poor feeding	Hypotonia, icterus	94	158	17/4.8	69	14	89	+	-	Absent/ Q188R
3/ M	5	Jaundice, poor feeding, lethargy	Hypotonia, icterus	116	98	16/5.1	80	16	56	+	-	Absent/ Q188R
4/ M	7	Seizure, jaundice	Hypotonia, encephalopathy, icterus	41	57	12/3.6	31	18	34	+	-	Absent/ Q188R
5/F	5	Jaundice, lethargy	Icterus	1432	582	13.6/4.7	68	83	149	-	-	Decreased/ Q188R
6/F	6	Jaundice, vomiting, jitteriness	Icterus	775	302	14/3.1	36	>360	187	+4	-	Decreased/ Q188R
7/M	1	Asymptomatic	Normal	31	9	2.9/0.38	75	12	28	-	-	Decreased/ Q188R

F: female; M: male; AST: aspartate aminotransferase (normal: 4-40 IU/L); ALT: alanine aminotransferase (normal: 10-55 IU/L); TB: total bilirubin (normal: 0.2-1.0 mg/dL); DB: direct bilirubin (<20% of TB); Blood glucose (normal: 50-90 mg/dL); PT: prothrombin time (normal: 11-15 sec); APTT: activated partial thromboplastin time (normal: 25-35 sec); URS: urinary reducing substances (normal: negative); CRP: C-reactive protein (normal: <1 mg/L); GALT: Galactose-1-phosphate uridyl transferase (normal: >3.00 U/g Hb); GALT activity were defined as GALT activity <5%, Gal-1-P >2 mg/dL

Discussion

The global incidence of classic galactosemia is estimated to range from 1 in 40.000 to 1 in 80.000 live births and occurs with equal frequency in both genders [3]. In our cohort, the female-to-male ratio was 4:3. Waggoner et al. identified jaundice and vomiting as the most prevalent clinical manifestations in a series of 350 patients [11]. Consistent with this, jaundice and feeding difficulties were the most common presenting symptoms in our cases. Hepatomegaly and abnormal liver function tests are frequently observed. In the early neonatal period, hepatic dysfunction often presents with jaundice dominated by direct hyperbilirubinemia, coagulopathy, and hypoglycemia. Management may require phototherapy or exchange transfusion due to severe hyperbilirubinemia. In some infants, hepatic complications such as ascites and cirrhosis may develop during infancy [1-5]. Among our patients, five exhibited elevated liver enzymes, marked hyperbilirubinemia necessitating phototherapy, elevated direct bilirubin levels, and prolonged coagulation tests requiring fresh frozen plasma replacement. One patient was admitted on the seventh postnatal day due to hypoglycemic seizures. Persistent, treatment-resistant hypoglycemia controlled only with intravenous high dose glucose infusion, alongside findings of direct hyperbilirubinemia, prompted further investigation, which led to a definitive diagnosis of galactosemia. Hypoglycemia is usually not a primary manifestation of classic galactosemia, since the inability to convert galactose to glucose does not cause hypoglycemia. However, lethargy, poor feeding, and liver dysfunction can result in hypoglycemia, as it could in any infant with these problems [15]. Renal tubular dysfunction—most notably proximal renal tubular acidosis—may manifest with aminoaciduria, proteinuria, and galactosuria [16]. In this respect, URS were detected in five of our cases. Without prompt elimination of dietary lactose, clinical deterioration may be rapid, often resulting in death within the first six weeks of life in the absence of appropriate supportive care [17]. The most frequent causes of mortality include hepatic failure, hemorrhagic complications, and sepsis, particularly due to *E.coli* [11]. Notably, galactosemia should be considered in the differential diagnosis of neonatal *E.coli* sepsis [12]. One of our cases presented with severe late-onset neonatal sepsis, and blood cultures confirmed *E.coli* growth.

Diagnostic confirmation of classic galactosemia is based on a GALT enzyme activity level below 5% and erythrocyte galactose-1-P concentrations exceeding 2 mg/dL [18]. The presence of non-

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glucose-reducing substances in the urine supports the diagnosis. The three most common mutations in the GALT gene are Q188R, K285N, and L195P [19]. All of our cases demonstrated GALT activity below 5%, consistent with classic galactosemia and all of them were found to carry the Q188R mutation. Seyrantepe et al. have reported Q188R as the most prevalent mutation among Turkish children [20]. Similarly, in a study reported by Atik et al. the most common genetic abnormality in 14 Turkish children was Q188R mutation [21]. Prenatal diagnosis is available and counseling should be provided before conception to parents with a family history of galactosemia or a previously affected child. Prenatal diagnosis can be made by GALT assay in fibroblasts cultured from amniotic fluid or chorionic villus biopsy or mutation analysis of DNA extracted from chorionic villus biopsy if the genotype of the index case is known [22]. Despite the presence of consanguinity between the parents and a known history of galactosemia in a sibling, the mother was not provided with counseling or offered the opportunity for prenatal diagnostic testing.

The main goal of treatment is to minimize dietary galactose intake. Galactose should be excluded from the diet as soon as the diagnosis is suspected. Other initial care should be provided to treat jaundice, sepsis, and other organ failure. Supportive therapy typically includes intravenous hydration, antibiotics, and treatment of coagulopathy, although problems usually resolve quickly after dietary treatment is begun [13]. Accordingly, all patients were initiated on a lactose-free diet during the early neonatal period, which led to marked clinical improvement and normalization of laboratory parameters within one week. Furthermore, to mitigate both acute and long-term complications, timely and comprehensive supportive interventions were implemented, including management of jaundice, hepatic insufficiency, coagulopathy, hypoglycemia, and sepsis.

Despite the prevention of acute metabolic crises, classic galactosemia remains associated with long-term neurological and developmental sequelae, even in patients diagnosed and treated during the neonatal period. Studies have reported that up to 80% of affected individuals may develop speech dyspraxia, cognitive delay, or fine and gross motor dysfunction later in life [23-25]. Ovarian failure in females, learning disabilities, and behavioral difficulties are also frequently described [26,27]. These outcomes are thought to result from persistent intracellular galactose-1-P accumulation and secondary alterations in glycosylation, despite strict dietary control [23,24]. Therefore, early diagnosis must be followed by multidisciplinary long-term follow-up involving metabolic specialists, neurologists, endocrinologists, and developmental therapists to optimize neurodevelopmental and psychosocial outcomes. Prospective longitudinal studies are warranted to better define the long-term benefits of early detection and dietary management, and to explore adjunctive therapeutic strategies aimed at improving neurological prognosis.

Despite the availability of carrier screening and prenatal diagnosis, classic galactosemia remains more prevalent in countries like ours, where consanguineous marriages are relatively common. Nonetheless, the disorder is not yet included in the routine national newborn screening program, often resulting in delayed diagnosis. It has been demonstrated that newborn screening performed within the first five days of life can prevent the acute decompensation associated with classic galactosemia [28]. Even in countries where such screening is implemented, early diagnosis is typically contingent upon clinical suspicion. In the absence of clinical awareness, severe symptoms may emerge before screening results are available [14]. A study by Berry et al. reported that, following the inclusion of galactosemia in the U.S. newborn screening program, the number of clinically severe cases decreased dramatically [3]. In our series, early diagnosis within the first week of life was achieved solely through clinical suspicion. Consequently, mortality related to liver failure, coagulopathy, early neonatal sepsis, and hypoglycemia was effectively averted. Moreover, it is believed that appropriate dietary management and supportive care have helped to minimize long-term morbidity.

Although classic galactosemia has a higher prevalence in our population compared to developed countries, the lack of early diagnosis underscores its significance as a public health concern. We advocate for the inclusion of galactosemia in the national newborn screening program and emphasize the importance of clinician awareness, given that this condition is entirely treatable through dietary intervention alone.

Conclusion

In conclusion, early diagnosis of classic galactosemia within the first week of life is crucial for preventing severe hepatic, neurological, and metabolic complications. In our case series, prompt recognition based on clinical suspicion and immediate initiation of a lactose-free diet resulted in rapid clinical and biochemical improvement in all infants. These findings reinforce the necessity of including galactosemia in the national newborn screening program, particularly in populations with high consanguinity rates. Early detection through screening or vigilant clinical assessment can significantly reduce mortality and long-term morbidity.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical Approval
Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Izmir Bakircay University (approval number:2365)

References

1. Berry GT, Segal S, Gitzelmann R. Disorders of Galactose Metabolism. In: Fernandes J, Saudubray M, van den Berghe G, Walter JH. Inborn Metabolic Diseases - Diagnosis and Treatment. 4th edition. New York: Springer-Verlag, Inc. 2006;78.

2. Fridovich-Keil J, Walter. Galactosemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D. The Metabolic and Molecular Bases of Inherited Disease. 8th

DOI: 10.5455/medscience.2025.09.249

edition. New York: McGraw-Hill Medical Publishing Division. 2008;72.

3. Berry GT. Classic galactosemia and clinical variant galactosemia. In: GeneReviews®. University of Washington, Seattle, Seattle (WA). 1993.
4. Anderson S. GALT deficiency galactosemia. MCN Am J Matern Child Nurs. 2018;43:44-51.
5. Bosch AM. Classical galactosaemia revisited. J Inherit Metab Dis 2006;29:516-25.
6. Murphy M, McHugh B, Tighe O, et al. Genetic basis of transferase-deficient galactosaemia in Ireland and the population history of the Irish Travellers. Eur J Hum Genet. 1999;7:549.
7. Hirokawa H, Okano Y, Asada M, et al. Molecular basis for phenotypic heterogeneity in galactosaemia: prediction of clinical phenotype from genotype in Japanese patients. Eur J Hum Genet. 1999;7:757.
8. Fedakar A, Dursun F, Ceyhan İ, et al. Galactosemia. Göztepe Tıp Dergisi. 2004;19:248-50.
9. Öztürk Y, Erdur B, Tokgöz Y. Clinical features of the patients with classic galactosemia. Türkiye Klinikleri J Pediatr 2010;19:16-9.
10. Bennett MJ. Galactosemia diagnosis gets an upgrade. Clin Chem 2010;56:690-2.
11. Waggoner DD, Buist NR, Donnell GN. Long-term prognosis in galactosaemia: results of a survey of 350 cases. J Inherit Metab Dis. 1990;13:802.
12. Barr PH. Association of escherichia coli sepsis and galactosemia in neonates. J Am Board Fam Pract. 1992;5:89-91.
13. Welling L, Bernstein LE, Berry GT, et al. International clinical guideline for the management of classical galactosemia: diagnosis, treatment, and follow-up. J Inherit Metab Dis. 2017;40:171-6.
14. Succoio M, Sacchettini R, Rossi A, et al. Galactosemia: biochemistry, molecular genetics, newborn screening, and treatment. Biomolecules. 2022;12:968.
15. Walter JH, Collins JE, Leonard JV. Recommendations for the management of galactosaemia. UK Galactosaemia Steering Group. Arch Dis Child. 1999;80:93.
16. Müller D, Santer R, Krawinkel M, et al. Fanconi-Bickel syndrome presenting in neonatal screening for galactosaemia. J Inherit Metab Dis 1997;20:607.
17. Karadag N, Zenciroglu A, Eminoglu FT, et al. Literature review and outcome of classic galactosemia diagnosed in the neonatal period. Clin Lab 2013;59:1139-46.
18. Ridel KR, Leslie ND, Gilbert DL. An updated review of the long-term neurological effects of galactosemia. Pediatr Neurol. 2005;33:153.
19. Leslie ND, Immerman EB, Flach JE, et al. The human galactose-1-phosphate uridyltransferase gene. Genomics. 1992;14:474.
20. Seyrantepe V, Ozgüç M, Coşkun T, et al. Identification of a mutation in the galactose-1-phosphate uridyltransferase gene in 16 Turkish patients with galactosemia, including a novel mutation of F294Y. Hum Mutat 1999;13:339-45.
21. Atik SU, Gürsoy S, Koçkar T, et al. Clinical, molecular, and genetic evaluation of galactosemia in Turkish children. Turk Arch Pediatr 2016;51:204-9.
22. Jakobs C, Kleijer WJ, Allen J, Holton JB. Prenatal diagnosis of galactosemia. Eur J Pediatr. 1995;154:S33.
23. Hughes J, Ryan S, Lambert D, et al. Outcomes of siblings with classical galactosemia. J Pediatr. 2009;154(5):721-726.
24. Waisbren SE, Potter NL, Gordon CM, et al. The adult galactosemic phenotype. J Inherit Metab Dis. 2012;35:279-86.
25. Ridel KR, Leslie ND, Gilbert DL. An updated review of the long-term neurological effects of galactosemia. Pediatr Neurol. 2005;33:153-61.
26. Rubio-Gozalbo ME, Haskovic M, Bosch AM, et al. The natural history of classic galactosemia: lessons from the GalNet registry. Orphanet J Rare Dis. 2019;14:86.
27. Welling L, Bernstein LE, Berry GT, et al. International clinical guideline for the management of classical galactosemia: diagnosis, treatment, and follow-up. J Inherit Metab Dis. 2017;40:171-6.
28. Badiu Tișa I, Achim AC, Cozma-Petruț A. The importance of neonatal screening for galactosemia. Nutrients. 2022;15:10.