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# Evaluation of our newborns with galactosemia

## Galaktozemili yenidoğan olgularımızın değerlendirilmesi

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**Abstract**

**Objective:** In this study, we aimed to help clinicians in the recognition and follow-up of galactosemia by emphasizing that this disease may manifest with different clinical pictures in the neonatal period

**Materials and Methods:** This retrospective uncontrolled study included 19 patients diagnosed with galactosemia and followed-up between January 1994 and January 2014. Five of them had been previously diagnosed. Reductant agents in urine were evaluated using Benedict test, while galactose-1-phosphate uridyltransferase (GALT) was measured with kinetic, enzymatic, colorimetric measurement method. GALT mutation analysis was performed with the Tetra-primer Amplification Refractory Mutation System-Polymerase Chain Reaction (ARMS-PCR) method. Galactose and free galactose were studied with the modified Diepenbrock colorimetric microassay method.

**Results:** Eight (42.1%) of the patients were female and 11 (57.9%) male. Time of the suspicion for galactosemia was found as 11.5±6.3 days, while one patient (5.3%) had a familial history of galactosemia. The most common findings were nutritional intolerance (n=17, 89.5%), hypotonia (n=17, 89.5%) and organomegaly (n=15, 78.9%). The most commonly seen genetic disorder was GALT enzyme deficiency (n=12, 85.7%) and the most common mutation was the Q188R mutation (n=8, 66.6%).

**Conclusion:** Galactosemia is a life threatening, but treatable disease with early diagnosis as well as being one of the metabolic diseases which cause confusion when clinically nonspecific findings are observed. Besides these clinical and laboratory findings, early diagnosis can be established by keeping in mind that galactosemia may present in infants having these findings.

**Keywords:** Galactosemia; Neonate; Clinical And Laboratory Findings.

**Öz**

**Amaç:** Bu çalışmada, galaktozeminin yenidoğan döneminde farklı klinik tablolar ile ortaya çıkabileceğini vurgulayarak hastalığın tanınmasında ve izlenmesinde klinisyenlere yardımcı olmayı amaçladık.

**Gereç ve Yöntemler:** Çalışmamız retrospektif kontrolsüz olarak planlandı. Ocak 1994 ile Ocak 2014 tarihleri arasında galactosemia tanısı konularak takip edilmiş ondokuz hasta çalışmaya alındı. Bu hastaların beş tanesi eski tanısı konmuş hastalardı. İdrarda redüktan madde Benedict testiyle, galactose-1-phosphate uridyltransferase (GALT) ölçümü kinetik, enzimatik kolorimetrik ölçüm metoduyla, GALT mutation analizi Tetra-primer Amplification Refractory Mutation System-Polimeraze Chain Reaction (ARMS-PCR) metodu ile galaktoz ve serbest galaktoz ölçümleri modifiye Diepenbrock kolorimetrik mikroassay yöntemiyle çalışıldı.

**Bulgular:** Hastaların 8 (%42,1) kız 11 (%57,9) erkek idi. Galaktozemiden şüphelenme zamanı 11.5±6.3 gün ve ailede galaktozemi hikayesi 1 (%5,3) hastada vardı. En fazla tesbit edilen bulgular beslenme intoleransı (n=17, %89,5), hipotoni (n=17, %89,5), organomegali (n=15, %78,9) olarak dikkat çekti. En fazla görülen genetik bozukluk olarak GALT enzim eksikliği (n=12, %85,7) ve en fazla görülen mutasyon Q188R mutasyonu (n=8, %66,6) olarak bulundu.

**Sonuç:** Galaktozemi hayatı tehdit eden ancak erken tanı ile tedavi edilebilen bir hastalık olamasının yanında, klinikte nonspesifik bulgular görüldüğünde tanısında kafa karışıklığına neden olabilen metabolik hastalıklardan biridir. Tüm bu klinik ve laboratuar bulgularının yanında, galaktozemi hastalığının bu bulguları taşıyan yenidoğanlarda akla getirilebilmesi de erken tanıyı sağlayabilir.

**Anahtar Kelimeler:** Galaktozemi; Yenidoğan; Klinik ve Laboratuar Bulgular.

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## INTRODUCTION

Galactosemia is an autosomal recessive metabolic disorder which occurs as a result of the deficiency of enzymes that metabolize sugar galactose. Lifelong treatment of galactosemia is necessary to remove galactose containing nutrients from the diet (Lactose Free diet-LF) (1-4).

Galactosemia occurs due to the lack of one of three enzymes involving the metabolism of galactose in the liver (Leloir pathway). Different clinical pictures may manifest in the lack of these enzymes. Diagnosis of the disease can be delayed if the disease manifest other rare findings. The most frequent and common enzyme deficiency in galactose metabolism is galactose-1-phosphate uridyltransferase (GALT). Clinical picture of galactosemia seen in GALT deficiency is called classic galactosemia (CG). The incidence of CG in Western Europe is estimated to be between at 1/23.000 and 1/44.000 (1,2,5,6).

Neonates with galactosemia are usually normal at birth. Clinical findings such as inadequate weight gain, nutritional intolerance, vomiting, organomegaly, diarrhea and hypotonia appear a few days after newborns begin to breastfeed. These clinical findings are common for many other diseases in newborns. Therefore, the first step in the diagnosis of galactosemia considering the disease is presence of clinical suspicion. However, manifestation of different clinical findings are frequent in the presentation or follow-up of the patients, which is the main delaying factor in the recognition of the disease (3,4).

Case reports in the literature that would facilitate identification of newborns with galactosemia, providing early diagnosis are very limited. Herein, we presented our experience and data of the patients with galactosemia followed for the past 20 years in the light of the literature. Thus, we aimed to provide support for both the patients and clinicians who treat these patients.

## MATERIAL and METHODS

The study was conducted on patients hospitalized in the NICU of Erciyes University Medical Faculty, Department of Pediatrics, Division of Neonatology in Kayseri, Turkey from January 1994 to January 2014. The study was designed as an uncontrolled retrospective study. Our NICU is a reference centre especially for the eastern and central region of Turkey where about 2000-2500 patients are hospitalized annually. A total of 19 patients who were followed-up in the neonatal service with the diagnosis of galactosemia were included in this study. The hospital computer database was screened to obtain data of the patients with galactosemia. The clinical and laboratory data of the patients were recorded.

Hepatomegaly was defined by ultrasonography. Acute renal failure was defined as serum creatinine level of more than 1.5 mg/dL. Conjugated hyperbilirubinemia in a neonate was defined as a serum conjugated bilirubin concentration of greater than 1.0 mg/dL if the total serum bilirubin is < 5.0 mg/dL or greater than 20% of the total serum bilirubin (7,8).

Clinical data were evaluated according to a standardized protocol. For neonatal history, medical records and interviews with parents were used. Ophthalmological examinations with a slit lamp were performed at the time of diagnosis.

Positive urine reductant sugars were used to screen for galactosemia (Benedict test). Diagnosis of classic galactosemia was performed by using the measurement of GALT activity in erythrocytes. Gas chromatography was used to detect galactose and galactitol substances in the urine (1).

Patients with a positive Benedict test underwent urine sugar gas chromatography and the diagnosis of galactosemia was established upon wide galactose band seen in this test (6,9,10). All the patients in the study were diagnosed in this method and recorded in the computer recording system of our hospital.

Tandem-mass spectrometry was considered positive if total galactose was higher than 10 mg/dL'den, free galactose was higher than 5 mg/dL or galactose-1-phosphate was higher than 5 mg/dL. Whereas, a GALT enzyme activity lower than 3 U/g Hb was accepted as pathologic. We performed GALT mutation analysis in the cases with low GALT activity. We studied Q188R, N314D (Duarte variant) and S135L in the GALT mutation analysis.

In several studies, a blood glucose value <40 mg/dL after the third day has been accepted as hypoglycemia (11). In the present study, we also followed this criterion for the diagnosis of hypoglycemia.

We established the diagnosis of liver failure in the cases of detected coagulopathy, hypoglicemia, hypoalbuminemia, hypofibrinogenemia, thrombocytopenia and low levels of aminotransferase (12, 13).

**Laboratory Methods;**
GALT measurement is a kinetic, enzymatic and colorimatic measurement based on the consumption of Uridine Diphosphate-Glucose (UDPG) (uridine-5' diphosphoglucose). Conversion of Nicotinamide Adenine Dinucleotide Phosphate (NADP) formed in the media to NADPH is based on the Beutler method in which it is converted to a color component in the presence of tetrazolium salt, allowing kinetic quantitation.

GALT mutation analysis was studied after the GALT biochemical test. Wild type allele and mutant allele were concurrently amplified with PCR reaction in the presence of internal control using the Tetra-primer Amplification Refractory Mutation System-Polimeraze Chain Reaction (ARMS-PCR) method. The distinction was made with normal agarose gel electrophoresis according to the differences in the length of amplicons.

Galactose and free galactose measurements were studied with the modified Diepenbrock colorimetric microassay.

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**Statistics;** Data were analyzed and evaluated utilizing SPSS 16.0 (IBM Corp., Armonk, NY) software. The evaluations are presented using 'descriptive statistics (Percentile values and distribution)'. The frequencies were calculated as number and percentage and the numerical data as mean±SD.

**Exclusion criteria;** We could not reach the definitive records of some patients diagnosed with galactosemia. Whereas, some of patients were diagnosed only with the Benedict test and died in a short time. The diagnoses of these patients were recorded as postmortem galactosemia in the patient recording system. Since the diagnosis of galactosemia was not consistent, we did not consider it appropriate to include these patients in our study.

## RESULTS

A total of 19 patients were included in this study with 8 (42.1%) being female and 11 (57.9%) male. The mean gestational age of our patients with galactosemia was found as 37.4±2.0 weeks (Table 1). Five patients had a familial history of sibling death (26.3%) (Table 1). A history of sibling death from galactosemia was found in one of these five patients. In the familial history of this patient with the sibling death from galactosemia, 4 siblings had died from unknown reasons within the first 4 months of life.

The delivery type of our patients was usually vaginal delivery 16 (84.2%). Maternal age was calculated as 29.5±4.5 years. Whereas number of total deliveries was found as 2.2±0.9 per person in mothers of the patients diagnosed with galactosemia (Table 1).

**Table 1.** Demographic Values

| **Gestational age (week)** (mean±SD) | **Gender F/M** | **Birth length(cm)** (mean±SD) | **Gestational weight (g)** (mean±SD) | **Birth Head circumference (cm)** (mean±SD) | **The story of brothers death** | **Type of delivery** (Normal/CS) | **Maternal age (years)** (mean±SD) | **Family history of galactosemia** | **Birth order** (mean±SD) | **When suspicion of galactosemia (day)** (mean±SD) | **Consanguine-ous marriage** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 37.4±2.0 | 8(42.1%)/ 11(57.9%) | 52.0±2.1 | 2975.7±323.8 | 33.7±1.6 | 5(26.3%) | 16(84.2%)/ 3(15.8%) | 29.5±4.5 | 1(5.3%) | 2.2±0.9 | 11.5±6.3 | 8(42.1%) |

Fifteen patients (78.9%) were found to present with the complaint of jaundice (Table 1). Time of suspicion for galactosemia was found as 11.5±6.3 days (Table 1). The latest time of galactosemia suspicion was on the 27$^{th}$ day and the earliest was on the 4$^{th}$ day. According to the hospital records, it was remarkable that the patients diagnosed upon the suspicion of galactosemia after 14. days of their lives died, but those diagnosed before 14 days survived. The patient with the latest time of suspected galactosemia and restricted diet (LF diet) was aged 12 days. Parents of eight patients had consanguinity marriage (42.1%) (Table 1).

Among the clinical findings, organomegaly was seen in 15 (78.9%), hypotonia 17 (89.5%) and nutritional intolerance in 17(89.5%) patients. These findings were the most frequently encountered findings in this study (Table 2).

**Table 2.** Clinical Findings

| **Cataract** | **Sepsis** | **Organo megaly** | **Ascites** | **Pseudotumor cerebri** | **Hypotonia** | **Seizures** | **The number of patients presenting with jaundice** | **Feeding intolerance** | **Renal failure** | **Life/Ex** |
|---|---|---|---|---|---|---|---|---|---|---|
| 8(42.1%) | 2(63.2%) | 15(78.9%) | 8(42.1%) | 2(10.5%) | 17(89.5%) | 3(15.8%) | 15(78.9%) | 17(89.5%) | 7(36.8%) | 12(63.2%)/7 (36.8%) |

We identified sepsis in 12 (63.2%) patients (Table 2). Escherichia coli (E.coli) sepsis was found in 8 patients, while no any pathogen was isoled in the remaining patients. Seven of the patients with E.coli detected were diagnosed late and all these patients were lost. Whereas, all four patients with unknown reason of sepsis survived.

Cataract was found in 8 (42.1%) patients (Table 2). Nuclear cataract was found in two and lenticular cataract in six patients. Majority of the patients with cataract identified was those detected in early period and put on LF diet, without are quirement for surgical operation. One patient with suspected galactosemia on the 17$^{th}$ day of life which could not be operated because of poor general condition died in a short time later although the patient was in need of eye surgery.

Pseudotumor cerebri (PC) was found in 2 (10.5%) patients (Table 2). One of these patients had previously been diagnosed with only Benedict test and sugar chromatography. The patient was detected to have PC in the clinical evaluation however we could not perform enzyme analysis in that time. The subject was admitted to our hospital approximately 20 years ago. This matter was discussed by the authors and it was suggested that there was no drawback to include this subject into the study as a patient with GALK enzyme deficiency and the subject was included as a subject with galactosemia in the study accordingly. Whereas GALK enzyme deficiency was found in the other patient who did not have finding of PC. Cataract was identified in both patients with PC. Convulsion was detected in 3 patients (15.8%) and two of them had GALK enzyme deficiency.

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Ascites was found in 8 (42.1%) patients (Table 2). This symptom was seen in only one patient as an initial clinic

symptom. This patient was the one who received treatment at 12th day of life and survived. This patient received spironolactone only over 3 days for ascites. Patient's ascites returned to normal within 4 days after diet therapy. Although ascites was observed in postmortem cases, no abnormal finding was found in the examination of ascites fluid.

Renal failure was seen in 7 (36.8%) patients who were usually died (Table 2). None of the patients had renal failure finding as an initial finding. However, renal failure was more common in the patients with end stage galactosemia.

Seven (36.8%) of our patients were lost. However, a remarkable detail in these cases was that almost all of the patient who died were those with suspected galactosemia in the late period and thus the treatment was initiated late.

Enzyme deficiency was only studied in total 14 (73.6%) of 19 patients since 5 (26.4%) patients were applied before the hospital obtained facility for enzyme determination. Among the patients with enzyme deficiency, GALT was found in 12 (85.7%) and GALK enzyme deficiency was found in 2 (14.3%) patients. Mutation analysis was performed for the patients with enzyme deficiency, Q188R was found in 8 (66.6%) patients and N314D (Duarte variant) was found in 2 (16.6%) patients, while no mutation was observed in 2 (16.6%) (Table 3).

Since the presentation of 5 patients was back-dated, the diagnosis was established only with reductant agent and sugar choromatography in urine. Furthermore, postmortem liver biopsy was performed in two of these five patients. Tandem mass could not be used to examine 5 patients with galactosemia, their diagnoses was established with Benedict test and urinary choromatography. Positive results were found in 10 (71.4%) of 14 patients underwent tandem mass examination (Table 3).

**Table 3.** Laboratory Findings

| **GALT Mutation** (Q188R/ N314D/ mutation could not be determined ) | **Enzyme deficiency** (GALT/ GALK) | **Tandem-mass positivity** | **Reduced sugar in urine (Benedict test)** | **Urinary sugar chromatography** | **Hypoglycemia** | **Direct bilirubinemi with the number of patients** | **TSH (mU/L)** (mean± SD) | **fT4 (ng/dl)** (mean± SD) | **Treatment of hypothyroidism** | **AST (U/L)** (mean± SD) | **ALT (U/L)** (mean± SD) | **İndir-bil (mg/dL)** (mean± SD) | **Dir-bil (mg/dL)** (mean± SD) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8(66.6%)/ 2(16.6%)/ 2(16.6%) | 12(85.7%)/ 2(14.3%) | 10(71.4%) | 11(57.9%) | 11(57.9%) | 8(42.1%) | 8(42.1%) | 15.7±15.4 | 1.19±0.3 | 2(10.5%) | 178.1±82.2 | 142±102.5 | 10.6±5.1 | 2,3±1.3 |

The Benedict test yielded positive results in 11 (57.9%) patients (Table 3). Five of the patients were the patients in whom enzyme determination could not be made. The remaining 5 of 6 patients were those with a poor condition and diagnosed in the late period.

Hypoglycemia was found in 8 (42.1%) patients (Table 3). Three of the patients with hypoglycemia had a poor general status. All of the hypoglycemic cases had nutritional intolerance. The first marked finding of three patients with suspected galactosemia was hypoglycemia. Thyroid-Stimulating Hormone (TSH) level was found as 15.7±15.4 mU/L and free-Thyroxine (fT4) level as 1.19±0.3 ng/dl (Table 3). Two patients were put on L-thyroxin therapy.

The number of patients with direct hyperbilirubinemia was found as 8 (42.1%) (Table 3). In terms of hepatic functions, Aspartate aminotransferase (AST) was found as 178.1±82.2 U/L, alanine aminotransferase (ALT) as 142±102.5 U/L, indirect-bilirubin levels as 10.6±5.1 mg/dL and direct-bilirubin levels as 2.3±1.3 mg/dL (Table 3). The patients with liver failure were usually those we lost and AST and ALT levels in these patients were either normal or lower than the mean values of the study.

Indirect hyperbilirubinemia is very common in the neonatal period. In addition, quite different factors may play a role in its etiology. Therefore we thought that indirect hyperbilirubinemia is not very useful to clinicians for early diagnosis of galactosemia and thus we did not clinically include in hyperbilirubinemia finding the the present study.

## DISCUSSIONS

Galactosemia is a metabolic disorder which can be efffectively treated if diagnosed promptly, but can be fatal if remaines unrecognised. The main source of galactose is lactose which is the main carbohydrate of the infant diet. Lactose consists of glucose and galactose. It is used as an energy source following convertion to glucose in the liver cells. First, galactose is phosphorylated to galactose-1-phosphate through galactokinase. Galactose-1-phosphate converts to glucose-1-phosphate and UDP-galactose through the GALT enzyme. In turn, UDP- galactose converts to UDP-glucose through uridine diphosphate galactose 4-epimerase (GALE). An inherited lack of one of these three enzymes causes galactosemia.

Galactose-1-phosphate accumulates especially in the liver, kidneys and brain and it is very toxic. It has classical, Duarte and heterozygous variants. Despite the fact that enzyme activity is decreased by 50% in the Duarte variant, the clinic picture is mild and usually does not require diet. GALT enzyme may have a wide range of mutations and accordingly clinical findings and complications may differ. Additionally, since more than one enzyme deficiencies can lead galactosemia and these enzymes can effect several organs, all these

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factors result in different clinical situations during manifestations of the disease (1,14-18).

By initiating a lactose and galactose restricted diet within the first 10 days of life, the symptoms may rapidly regress and liver failure, sepsis, mental retardation and death may be prevented. Since galactosemia may manifest signs of multiorgan failure, the most important stage in diagnosis of the disease is always to keep in mind the possibility of galactosemia (19-22).

In the patients diagnosed with galactosemia, galactose is removed from the diet (lactose free diet-LF). Soy-based milk or formulas are recommended in some countries while formulas containing casein hydrolyzates and maltose dextrin are recommended in others. Therefore, manifestation of the severe acute signs and late complications of galactosemia can be prevented (14,23,24).

However, despite LF diet therapy, long-term complications such as learning disability, growth retardation and psychomotor retardation may still be encountered (1,24,25).

The most common cause of galactosemia is GALT enzyme deficiency. Although numerous mutations of GALT enzyme have been identified, the most frequently seen mutant allelles are Q188R, K285N, S135L and N314D which is the Duarte allele (27). The GALT gene in humans is found in the p13 region of the 9th chromosome. Among about 40 mutations that have been identified, the most common is the Q188R mutation. Prenatal diagnosis may be possible with the measurement of galactitol in amniotic fluid, determination of GALT enzyme activity in chorionic villi and cultured amniocytes and mutation analysis (14,28). Common mutations can be detected by DNA analysis, but a negative result does not rule out the diagnosis of galactosemia because of the large number of GALT mutations (27).

The presence of reductant substances in the urine is sometimes suggested as a test for galactosemia. However, the gold standard for diagnosis of classic galactosemia is the measurement of GALT activity in erythrocytes (6, 9, 10, 21). Whereas, in the present study mutation could not be detected in two of the twelve patients with GALT deficiency, while in two other patients, it was thought that the disease could have resulted from an undefined mutation of GALT.

Data in the literature regarding whether there is a correlation between the genotype and phenotype of patients with CG are controversial. Some studies have demonstrated that partial GALT deficiency is not associated with the long and short term complications, while other studies have shown that partial GALT deficiency has an effect on the long and short term speech and language development (29-31).

In one study, IQ scores were found to be lower in subjects with homoallele Q188R mutation than in those with heteroallele Q188R, independently from metabolic control and sociodemographic characteristics (17). However, other studies have found no correlation between the phenotype and genotype in terms of loss in cognitive functions, neurological findings and ovarian failure (32,33). Therefore, mutation analysis may not be guiding for treatment and prognosis in persons with classical galactosemia. In our study, all of the patients were those carrying Q188R and N314D mutations.

Walter (21) reported that, determination of reductant agents in urine may be important in patients presenting with severely elevated levels of indirect billirubin. In our study, there were two patients suspected for galactosemia due to billirubin elevation and increased levels of AST and ALT. Duarte variant was detected in the mutation analysis of these two patients. The general laboratory status of both patients was rapidly resolved with LF diet and normal diet was initiated at the later periods with close monitoring of the patients.

In our patients, when reducing agent was detected in urine as specified in the literature, LF therapy was started until GALT enzyme activity results were obtained. Due to technical difficulties, galactosemia diagnosis was established with he Benedict test followed by urine chromotagraphy in patients who had been previously diagnosed.

In a study from our country, the diagnosis of galactosemia was established on average on the 13$^{th}$ day of life (34). Whereas in our study, the mean time for suspected galactosemia was found as 11.5±6.3 days. This result was consisted with the previous study.

Waggoner et al. (35) reported the most common clinical findings of galactosemia as jaundice by (74%), vomiting (47%), hepatomegaly (43%), growth retardation (29%), poor nutrition (23%), lethargy (16%), diarrhea (12%), sepsis (10%) and ascites (4%). In a study retrospectively investigating 22 patients with galactosemia from our country, hepatomegaly was found in 100%, jaundice in 86% (63% indirect, 36% direct), vomiting in 77% and nuclear cataract in 68% of patients (34). As these studies indicated obvious, clinical findings may largely vary.

There is susceptibility to sepsis, especially E.coli (76%) infections in galactosemia which can be seen within the first two weeks. Even it may occur before the diagnosis of galactosemia. The reason of frequently seen sepsis in galactosemia is that galactose and its metabolites inhibit the antibacterial activity of leukocytes. The other known common agents for sepsis include Klebsiella, Staphylococci and Streptococci (1,2,36,37).

In our country, the incidence of E.coli sepsis in galactosemia has been reported as 45% (34). Although rare, the association of galactosemia and invasive fungal infection has been reported in some case reports (38). None of our patients had fungal infection. Whereas sepsis was found in 12 patients (63.2%). E.coli sepsis was found in 8 (66%) of these patients, while no any pathogen was isolated in the remaining four patients.

Seven patients in whom E.coli was detected were those diagnosed late and all of them died lost. One patient was admitted to our clinic with the findings of end stage

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sepsis, kidney-liver failure and meningitis since early diagnosis could not be established and lost at the 18th hour of the life. E.coli was isolated in the blood culture collected from this patient in postmortem examination. All of the four patients without sepsis survived. In this respect, our study suggested that sepsis may be a poor prognostic finding in patients with galactosemia.

It has been reported in the literature that, nuclear cataract is more commonly developed in GALT deficiency, while lenticular cataract is more common in GALK deficiency. Nuclear cataract is usually bilateral and usually develops after to weeks of birth due to the deposition of galactilol in the lens. This condition is usually regressed upon diet therapy (39). In the present study, among 8 patients with cataract, lenticular cataract was found in 6 and nuclear cataract in 2 patients.

Lenticular cataract was seen in both patients with GALK deficiency. The reason behind less number of the patients with nuclear cataract was attributed to early identification of these patients. Whereas, the diagnosis was established in a late period in both patients with nuclear cataract. Cataract in patients with an early diagnosis was treated with LF-diet. In this aspect, our findings were in parallel to the literature reporting that lenticular cataract is more common in patients who are identified early with GALK deficiency. Only one patient required surgical cataract treatment, while the other cataract cases were under control with LF therapy.

Previous studies have reported that the determining of reducing agents in urine may be helpful in early diagnosis of galactosemia and in preventing complications in patients presenting with elevated indirect billirubin. There are studies in the literature demonstrating that besides direct billirubin, indirect billirubin may also be found in patients with galactosemia (7,20,21,34,40,41).

Related to the liver, direct hyperbilirubinemia, hyperammonemia, hepatocellular damage and cirrhosis may develop in galactosemia. Among our patients, 15 (78.9%) had been admitted due to the complaint of jaundice (Table 1). This rate is close to that reported by Waggoner (35) as 74%. However, in our cases the number of patients presented with direct hyperbilirubinemia was 42.1% (Table 3). The majority of these patients consisted of those who were identified in the late period and those who died. Therefore, our study suggested that direct billiribunemia can be considered as an end stage finding of galactosemia.

If galactosemia is caused by severe GALT deficiency, removing galactose from diet may not resolve liver failure. In addition, a diet poor in galactose may not be effective in prevention of long-term complications such as intellectual disability, mental retardation and ovarian failure in severe GALT deficiency (29-31). In our study, the 7 patients who died had the findings of liver failure. However, it was thought that some of these findings may have resulted from direct effects of galactosemia, and the others may have been caused by the secondary effects of sepsis.

In those patients who showed the findings of liver failure and died, the levels of AST and ALT values were either normal or close to those of the other patients. Elevated AST and ALT and billirubin were found in 7 of 12 patients who survived. AST and ALT values returned to normal within 2 months and billirubin within the first 2 weeks of life in all the survivors.

Ascites is a rarely seen problem in the neonatal period and a frequently may be of biliary, urinary or chylous origin. Genitourinary, cardiac, hepatic diseases and infections causing systemic involvement, such as TORCH and parvovirus infections and inherited metabolic diseases may be involved in the etiology as well as it may be idiopathic (42-44). Ascites is usually seen after the second week of life in galactosemia due to post-nutrition hepatocellular damage. However, occasionally this condition may develop within the first days of life and may be a remarkable prognostic finding in patients with galactosemia (35, 45). Ascites was determined in 8 (42.1%) patients (Table 2).

Whereas, rate of ascites has been given as 4% in the study by Waggoner (35). The reason of that great difference in the rate of ascites can be attributed to a large number of late diagnosed patients in our study. Among 8 patients with ascites in the study, 6 patients were at the terminal stage and died. In this respect, the finding was consistent with the literature reporting that ascites is a poor prognostic indicator (45). The other remaining two patients with ascites were treated with diet and spironolactone. One of these patients had only mild ascites which could be detected on ultrasonography and resolved with LF-diet. For all these reasons, our study demonstrated that it is very crucial to consider galactosemia in the differential diagnosis of neonatal ascites.

Looking at the literature, PC is an infrequent finding of galactosemia. The mechanism of the occurrence of PC is thought to be the increased galactitol concentration in BOS, resulting in increased oncotic pressure. Patients are lethargic due to increased intracranial pressure and cerebral edema is marked in the imaging of the central nervous system (39,42,46,47).

PC was found in 2 (10.5%) of the patients (Table 2). One of these was the patient who had been previously diagnosed and only the Benedict test and urine chromatography were used to establish the diagnosis. Therefore, information regarding enzyme deficiency in this patient could not be obtained, but GALK deficiency was considered as the possible diagnosis. However, in the other patient GALK enzyme deficiency was determined. These results are in keeping with the literature reporting that PC is more common in galactosemia due to GALK deficiency.

Convulsion was found in 3 (15.8%) patients (Table 2). Two of these patients had PC which was mentioned above. Additionally, cataract was also found in two of three patients with PC. In this respect, our study findings suggested that associations of PC, convulsion and cataract may be closely correlated in patients with galactosemia.

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It has been reported that galactose and its metabolities may also affect thyroid functions. This impairment may be due to deficiency of the thyroid binding globulin of which synthesis is deterioted because of the liver destruction by the toxic impact of galactose or its metabolites in classic galactosemia. A decreased level of fT4 with a normal level of TSH (transient hypothroxinemia) is frequently seen in preterm infants, but it is rare in term babies. In the literature, patients presenting with normal TSH and low fT4 levels have been reported more commonly. There are also reports that thyroid function returned to normal with galactose free diet in patients with hypothyroxinemia (48-51).

In our study, we administered thyroid replacement therapy in only two patients. These patients had high TSH and low fT4 values. One of these patients had been diagnosed after the 14$^{th}$ day. In the other patient, L-thyroxine treatment administered was discontinued after LF diet therapy.

Renal failure and renal tubular dysfunction may be seen in galactosemia (1,51). Mild tubulopathy was found in 3 patients who survived. In addition, all of the 7 patients who died had renal failure. None of the patients had renal failure as an initial symptom or early galactosemia symptom. Therefore, renal failure was considered as a late finding of galactosemia. Nevertheless, we concluded that renal failure seen in galactosemia may be due to the direct effect of galactosemia as well as secondary to the disease.

## CONCLUSIONS

Galactosemia is one of the life-threatening, but treatable diseases if diagnosed early. Patients with galactosemia may present with nonspecific findings in neonatal period. Nonspecific findings encountered during the clinical course may lead to confusion and delay in the diagnosis, thus causing delay for the treatment which is critical for the patient. Understanding of the infrequent clinical findings of galactosemia may facilitate in keeping the disease in the mind and establish an early diagnosis.

In this study, we aimed to provide support to clinicians in the diagnosis and follow-up of galactosemia by emphasizing that this disease may manifest with different clinical pictures in the the neonatal period.

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