Original Article

Türk Pediatri Arşivi
Turkish Archives of Pediatrics

Clinical, molecular, and genetic evaluation of galactosemia in Turkish children

Sezen Ugan Atik, Semra Gürsoy, Tuba Koçkar, Hasan Önal, Servet Erdal Adal

Clinic of Pediatrics, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey

Abstract

Aim: Galactosemia is a carbohydrate metabolism disorder with autosomal recessive inheritance. The most frequent enzyme deficiency is galactose-1-phosphate-uridylytransferase, which causes classic galactosemia. When the enzyme is absent, an infant cannot metabolize galactose-1-phosphate and it cumulates in liver, kidney, brain, tongue, lens, and skin. This study aimed to evaluate the clinical and molecular characteristics of patients with galactosemia, which is observed more frequently in our country than anywhere else in the world.

Material and Methods: This is a retrospective study that includes the moleculer and genetic charcteristics of 14 patient who were diagnosed as having galactosemia between January 2009 and January 2011.

Results: Nine patients were male and 5 female. Consanguineous marriage was detected in the family history of 7 patients. One patient had a history of a deceased sibling with a confirmed diagnosis of galactosemia. The main reasons for admission to the hospital were jaundice in 9, hypoglycemia in 2, sepsis in 2, and elevated liver enzymes in 1 patient. The Beutler test was positive in all patients. The mean enzyme activity was 0.36±0.26 μmol/mL. Only 6 of our cases were diagnosed in the early period (first 15 days). Cataract was present in four patients. Q188R mutation was observed in 13 patients, and homozygote N314D and homozygote E340X mutations were observed in one patient. Three patients had impaired neurologic development according to the Denver Developmental Screening Test II.

Conclusion: The most common genetic abnormality was Q188R mutation. Only 43% of our patients's disease could be diagnosed at an early stage. We suggest that galactosemia should be included in the national newborn screening program in order to make earlier diagnoses. (Turk Pediatri Ars 2016; 51: 204-9)

Keywords: Galactose-1-phosphate uridyltransferase deficiency, galactosemia, newborn screening

Introduction

Galactosemia is a congenital disorder caused by a deficiency of different enzymes in the metabolism of galactose, which is one of the monosaccharides. Three different enzymes are involved in the metabolism of galactose include galactose-1-phosphate uridyltransferase (GALT), galactokinase, and epimerase (1). The most common enzyme deficiency is galactose-1-phosphate uridyltransferase deficiency, which causes classic galactosemia (1). Its worldwide incidence ranges between 1/40 000 and 1/80 000 (2). Galactose-1-phosphate uridyltransferase deficiency (classic galactosemia) is inherited autosomal recessively. In seventy percent of the Caucasian race, Q188R and K285N missense mutations are present and related with severe morbidity (1). Screening for carriers and prenatal diagnosis may be realized by way of direct enzyme analysis in the amniocytes and chorionic villi or DNA-based tests may be performed. In the absence of galactose-1-phosphate uridyltransferase (GALT), patients cannot metabolize galactose-1-phosphate. Increased galactose-1-phosphate accumulates in the liver, kidney, brain, tongue, lens, and cutaneous fibroblasts, and causes injury. In many patients, jaundice, hepatosplenomegaly, hepatic failure, feeding difficulties, hypoglycemia, renal tubular dysfunction, muscular hypotonia, sepsis, and cataracts are observed following intake of galactose in the neonatal period (3, 4). Rapid symptom regression occurs with early initiation of treatment, but outcomes that affect

Address for Correspondence: Sezen Ugan Atik E-mail: sezenugan@hotmail.com
Received: 18.12.2015 **Accepted:** 19.07.2016

DOI: 10.5152/TurkPediatriArs.2016.3759

life negatively in the short and long term may be observed (1). Although the clinical picture mentioned above is found at one end of galactose-1-phosphate uridyltransferase deficiency, completely asymptomatic cases may be found at the other end. It is thought that this group of patients with partial transferase deficiency is observed more frequently compared with classic galactosemia. Most patients who are diagnosed as having galactosemia in neonatal screening programs are those with a high blood galactose level and/or reduced GALT enzyme efficiency. The fact that the disease manifests with varying degrees of clinical pictures may be explained by the different types of GALT enzyme, which is polymorphic.

Lactose, which is the main source of galactose, should be eliminated from the diet during treatment. Although limitation of galactose intake with the diet ameliorates the symptoms of feeding difficulty, hepatic dysfunction, muscular hypotonia, and cataract, it has been reported that disruption in cognitive functions, neurologic involvement, tremor, verbal apraxia, and hypergonadotropic hypogonadism (in girls) may occur in long-term follow-up under diet therapy (2). The predominating view is that these disorders are caused by long-term exogenous galactose exposure and endogenous galactose production in the prenatal period.

Close monitoring is necessary in patients with classic galactosemia because of all these factors mentioned above (3-5). These patients will remain on a special diet throughout their lives and it is recommended that they are followed up by a multidisciplinary team. This team should include a pediatrician experienced in metabolic diseases, a dietician, a neurologist, a child psychiatrist, a psychologist, an endocrinologist, an ophthalmologist, a speech therapist, and a specialist in genetics.

In this study, we aimed to evaluate the clinical, molecular, and genetic characteristics of patients with this congenital metabolic disease, which is observed more frequently in our country compared with the rest of the world.

Material and Methods

In this study, the outpatient clinic recordings of 14 patients who were diagnosed and followed up in the Ministry of Health Kanuni Sultan Süleyman Education and Research Hospital, Pediatric Nutrition and Metabolism Outpatient Clinic between 2009 and 2011 were used. Ethics committee approval was obtained from Bakırköy Women and Children's Education and Research Hospital Ethics Committee (29.4.2009/219). Written informed consent was obtained from the families of the patients. The sex, symptoms at initial presentation, the time between symptom onset and diagnosis, birth weights, degree of consanguinity between the mother and father, familial history of similar disease, and history of operation because of cataract were recorded. The presence of findings at presentation including jaundice, dehydration, cataract, sepsis, fever, seizure, hepatomegaly, and ascites was evaluated. The following laboratory findings at presentation were examined: total bilirubin (studied using spectrophotometry; normal: 0.2-1.0 mg/dL), AST (normal: 4-40 IU/L), ALT (normal: 10-55 IU/L), glucose (normal: 50-90 mg/dL). The prothrombin time was studied using a coagulometer (normal: 11-15 s), activated partial thromboplastin time (normal: 25-35 s) and potassium (normal: 3.5-5 mEq/L) and sodium (normal: 130-150 mEq/L) values studied by the "ion selective electrode" in terms of Fanconi syndrome were recorded. Peripheral smear, C-reactive protein and hemoculture results were examined in terms of sepsis. Presence of reducing substance in urine and presence of galactose in urinary sugar chromatography were recorded. The results of the Beutler test were evaluated. GALT enzyme efficiencies in the erythrocytes were measured using spectroflourometry in all patients for making the definite diagnosis (normal: 4-12 μmol/mL). *GALT1* gene mutations were investigated using exon 5, 6, 7, 9, and 10-specific E5F-E7R, E9F-E10R primers with DNA sequencing analysis in the peripheral blood samples. The body measurements (weight and height percentile values) of the patients during the follow-up period were recorded. Speech problems and mental developments were evaluated by the history taken from the family and Denver Developmental Screening Test II. In this study, the Statistical Package for the Social Sciences 10.0 (SPSS version Inc.; Chicago, IL, USA) was used for statistical analyses. All data are expressed as mean and standard deviation.

Results

Fourteen patients who were diagnosed as having galactosemia between the year of 2009 and 2011 were included in the study. Nine of our patients were male and five were female. The mean age was 35±29 months (range, 5 months-108 months) and the mean birth weight was 3230±640 grams. Different degrees of consanguinity were present between the mother and the father in seven patients. Consanguineous marriage was not present in the other seven patients. One patient had a family history of mortality of a sibling with galactosemia and another patient had a family history of a relative with galactosemia. First-degree consanguinity was present between the mother and father of a patient who had a family history of a lost sibling with galactosemia.

The mean age at the time of diagnosis was 17±8 days (range, 7-33 days). The reasons for hospitalization were as follows: jaundice in nine patients, hypoglycemia in two patients, sepsis in two patients, and increased transaminase levels in one patient (Table 1). The mean age at the time of

Table 1. Clinical and laboratory characteristics of patients with galactosemia

Patient number n=14	Abnormal coagulation tests	Increased hepatic function tests	Increased bilirubin	Sepsis	Hypoglycemia
1	+	+	-	-	-
2	-	-	+	+	-
3	-	-	+	-	-
4	+	+	+	-	-
5	+	+	-	-	+
6	+	-	+	-	-
7	-	+	+	-	-
8	-	-	+	-	-
9	+	+	-	-	+
10	-	+	+	-	-
11	+	-	-	+	-
12	+	+	+	-	-
13	+	-	+	-	-
14	+	+	-	-	-

diagnosis was 17±7.2 days in the patients who presented with jaundice, 22±2.8 days in the patients who presented with hypoglycemia, and 9.5±3.5 days in those who presented with sepsis. The highest total bilirubin level was found as 30 mg/dL in nine patients with jaundice. In the assessment performed in terms of Fanconi syndrome, electrolyte disturbance was not found in any of our patients.

At presentation, eight of our patients had feeding difficulties and eight had vomiting. On physical examination, hepatomegaly was present in eight patients and ascites was present in three patients. The laboratory tests of our patients are shown in Table 1. Nine of our patients had disrupted coagulation tests and eight had increased liver function tests.

The Beutler test was positive in all fourteen patients. The mean GALT enzyme efficiency was found as 0.36±0.26 μmol/mL. Four patients had cataracts at the time of diagnosis. In the follow-up of our patients, cataract regressed with diet therapy and surgery was not needed. Q188R mutation was found in 13 patients and homozygous N314D and homozygous E340X mutations were found in one patient (Table 2). Heterozygous N314D and E340X mutations were present in the parents of the patient with this mutation.

Table 2. Enzyme levels and genetic mutations in the patients with galactosemia

Patient number n=14	Enzyme level (μmol/mL)	*GALT* mutation
1	0,2	Q188R
2	0,48	Q188R
3	0,1	Q188R
4	0,3	Q188R
5	0,38	Q188R
6	0,8	Q188R
7	0,31	Q188R
8	0,53	Q188R
9	0,3	Q188R
10	0,9	Homozygous N314D / Homozygous E340X
11	0,4	Q188R
12	0	Q188R
13	0,1	Q188R
14	0,3	Q188R

The mean duration of hospitalization was 21±13 days (range, 6-50 days). Growth and development were examined in the mean follow-up time of 17 months (range, 4 months-2 years). At the final outpatient follow-up examination, body weight was found in the 3rd percentile in two patients, the 10th percentile in three patients, the 25th percentile in four patients, the 50th percentile in three patients, and in the 75th percentile in two patients. In the follow-up of height, height was found in the 3rd percentile in three patients, the 10th percentile in one patient, the 25th percentile in four patients, the 50th percentile in two patients, the 75th percentile in three patients, and in the 90th percentile in one patient.

In the final follow-up visit, neurologic development was evaluated using the Denver II Developmental Screening Test (DENVER II). DENVER II was found normal in eleven patients; one patient had delayed language and gross mo-

tor development; one patient had delayed personal social development, delayed fine motor development, and delayed language development; and one patient was found to have suspicious personal social development and delayed fine motor development. The mean age at the time of diagnosis was 15.09±6.2 days in 11 patients who had a normal DENVER II, and 27.67±6.8 days in three patients who had an abnormal DENVER II. One of our patients was being followed up because of epilepsy.

Discussion

Galactosemia is one of the carbohydrate metabolism disorders, which is inherited autosomal recessively. Although the disease is observed with the deficiency any of the three enzymes involved in the metabolism of galactose, GALT deficiency is observed most commonly. The worldwide incidence of classic galactosemia ranges between 1/40 000 and 1/60 000. In studies conducted in our country, the incidence was found as 1/23 775 (2, 5-7). In our study, the frequency of consanguineous marriage was 50%. In the study conducted by Öztürk et al. (6), the frequency of consanguineous marriage was similarly reported as 57.1%. In light of these data, the fact that this metabolic disorder is observed more frequently in our country compared with developed countries may be related with consanguineous marriages. It is clear that raising public awareness of this issue and preventing consanguineous marriages is necessary.

The ages at the time of diagnosis were examined in many studies, and patients who were diagnosed in the first 15 days were defined as early diagnosed (8-12). In our study, six of our patients were diagnosed in the first 15 days after birth and the remaining eight patients were diagnosed after 15 days. The mean age at the time of diagnosis was found as 17±8 days. Although the disease was symptomatic in the first weeks of life, a delay in diagnosis was observed. In a Turkish study conducted by Öztürk et al. (6), the age at the time of diagnosis was 28 days, which was similar to our data. In the study conducted by Karadağ et al. (8), it was reported that the mean age at the time of hospital presentation was 13 days. Henderson et al. (9) reported that 17 patients were diagnosed over a period of 21 years in the region of Cape Town in South Africa, the mean age at the time of diagnosis was 5.1 months. In the study conducted by Krantz et al. (10) with 148 patients between 1955 and 1995 in Germany, the rate of early diagnosis was reported as 57.8%. The rate of early diagnosis was recorded as 29% by Shah et al. (11), and 61.5% by Schweitzer et al. (12). The delay in diagnosis of this metabolic disease, which is not included in the neonatal screening program in our country, may be related with delayed presentation of patients, difficulty experienced by the primary care physician in making the diagnosis, and confusion of the clinical picture at the time of presentation with many other conditions.

The most common reason for presentation at the time of diagnosis was jaundice in our patients. Similarly, jaundice was also the most common finding in the study conducted by Öztürk et al. (6). In the study conducted by Karadağ et al. (8), jaundice was found in 86% of patients. However, patients with sepsis were diagnosed earlier compared with those followed up because of jaundice. Thus, we think that galactosemia should be considered when response to treatment is delayed in patients hospitalized in neonatal wards because of jaundice, not least because it is more prevalent in Turkey than in any developed countries.

Feeding difficulty and vomiting are observed commonly as a result of the clinical picture caused by the accumulated toxic metabolites in classic galactosemia. In this study, eight patients had feeding difficulties and six of these patients were vomiting in addition. Waggoner et al. (13) reported that among 240 patients, the frequency of feeding difficulty and vomiting was 76% and 47%, respectively. In classic galactosemia, clinical and laboratory findings related with liver disease are observed because of the toxicity caused by galactose-1-phosphate accumulated in the liver. At the time of presentation, abnormal coagulation tests were found in nine patients, increased transaminase values were found in eight, hepatomegaly was found in eight, and ascites was found in three. Shah et al. (11) reported the frequency of hepatomegaly as 41%, the frequency of jaundice as 82%, and the frequency of hepatic failure as 29%. In the study conducted by Coşkun et al. (14) with 18 patients, jaundice was reported with a rate of 77.7% and hepatomegaly was reported in 72.2% of patients. The most commonly involved organ is the liver in patients with galactosemia, in whom hepatomegaly and hepatic failure are reported frequently.

Ophthalmologic examinations should be performed carefully because cataracts are a common finding in patients with galactosemia. In our study, four patients had cataracts. In the follow-up of our patients, cataracts regressed with diet therapy and surgery was not required. In the study of Karadağ et al. (8), four patients underwent surgery because of cataracts. The mean age at the time of diagnosis was 17±2.8 days in our patients who were diagnosed with cataract. Cataract may improve when treatment is initiated in the first 2-3 weeks of life, but surgery is needed when treatment is delayed or when there is excessively increased opacity in the lens (1). Widger et al. (15) reported that cataract was found during follow-up in 14 of 100 patients with galactosemia. When compliance with diet was examined in these patients, no statistically significant relation was found between patients with and without cataracts.

The three classic mutations most commonly observed in the *GALT* gene include Q188R, K285N, and L195P (16). The most common *GALT* mutation in our patients was

the Q188R mutation and the mean enzyme level was found as 0.36±0.26 μmol/mL, which was found compatible with classic galactosemia. In a study with Turkish children by Seyrantepe et al. (17), the most common mutation was the Q188R mutation, as with our patients. In the genetic study conducted by Murphy et al. (18) with Irish patients, the predominant mutant allele that caused classic galactosemia was Q188R with a rate of 93.6%. Steven et al. (19) evaluated 76 cases of classical galactosemia in the region of Pennsylvania, and the Q188R mutation was found at a rate of 77.6%. In the present study, homozygous N314D, homozygous E340X mutation was found in one patient. It was found that the parents of the patient were first-degree cousins and carried heterozygous N314D and E340X mutation. It is notable that these consanguineous parents carried two different heterozygous mutations, which caused galactosemia. The N314D mutation is observed in the Duarte variant, which is more benign compared with classic galactosemia (20). The E340X mutation was first described by Gathof et al. (21) in 1995. They found N314D polymorphism accompanying E340X mutation in one of three patients who were found to have an E340X mutation. It was reported that the clinical prognosis was better in the patient who carried the polymorphism compared those with homozygous E340X. Shin et al. (20) showed that the N314D mutation was compound heterozygous in patients who carried E340X mutations and the enzyme level ranged between 0% and 0.5%. In the study conducted by Seyrantepe et al. (17) with 16 Turkish patients, one patient was found to have the E340X mutation. Schuster et al. (22) reported two Turkish patients from a single family who had galactosemia in 1998 in Germany, presence of E340X mutation was reported in one female patient who presented with a severe clinical picture and was followed up with mental retardation. In this patient, N314D polymorphism, which causes the Duarte variant, was also shown on the same allele as in our patient.

The mainstay of treatment in galactosemia is composed of elimination of galactose, a monosaccharide found in the structure of lactose. Breastmilk, cow's milk, and formulas contain a significant amount of lactose thus galactose; therefore, they should not be given to these patients. In infancy, formulas containing lactose-free casein hydrolysates or separated oligosaccharides can be used. Exogenous calcium and vitamin D supplementation is also required to prevent reduction in bone mineralization in patients with galactosemia. Patients with GALT and galactokinase deficiency are followed up with measurements of erythrocyte galactose-1-phosphate levels and urinary galactitol levels (23). During follow-up, growth of patients with galactosemia should be monitored closely as in our patients, and the weight and height values should be kept between the 10th and 90th percentiles appropriate for age. It has been reported that prenatal growth is normal, but postnatal growth is affected in galactosemia and this is related with decreased IGF-1 and IGF-BP-3 levels (24). Similar to the literature, the mean birth weight was found as 3230 g±640 g and prenatal growth was observed as normal. However, growth and developmental retardation was not found in the follow-up of our patients. It is thought that this may have arisen from the fact that the age distribution of our patients was relatively narrow (5-108 months) and long-term follow-up is required for a more definite judgement. Patients should also be closely monitored in terms of neurologic, endocrinologic, and psychosocial aspects. When the patients were evaluated with DENVER II in accordance with these recommendations, motor and personal social developmental retardation was found, but IQ values could not be measured. In the study of Shield et al. (25) with 34 patients, the mean total IQ was 79, the mean performance IQ was 79, and the mean verbal IQ was determined as 82. In their study, it was reported that mental retardation was related with genotype rather than metabolic control. Some studies emphasized that mental retardation and neurologic complications were not only related with genotype or galactose-1-phosphate level and other factors may be involved (26). IQ assessment could not be performed in our study because the mean age of our patients was 36 months and long-term follow-up is necessary to determine IQ values.

In the United States of America (USA) and in many countries in Europe, galactosemia has been included in neonatal screening programs. In our country, phenylketonuria, congenital hypothyroidism, biotinidase deficiency, and cystic fibrosis are included in the neonatal screening program, but galactosemia has not yet been included in this scope. In the article of Porta et al. (27), in which they shared their 30-year experience, it was emphasized that neonatal screening performed in the first five days prevented acute worsening related with classic galactosemia. In another study conducted in the USA, it was reported that very few patients with a worsened clinical picture due to galactosemia were seen after galactosemia was included in the screening program (28). Polak et al. (29) reported that the neonatal screening program conducted in Austria enabled detection of this rare disease in many newborns. In a cost-effectiveness study conducted in Brazil, inclusion of galactosemia in the neonatal screening program was found more cost-effective (30). Although the disease is symptomatic in the first weeks, accurate diagnosis is considerably delayed in our country, as seen in this study. The fact that the diagnosis is delayed in our country, even though it is observed more commonly compared with developed countries, renders galactosemia a significant public disease. We think that inclusion of galactosemia in the national neonatal screening program will be a realistic solution for this public problem.

Ethics Committee Approval: Ethics committee approval was received for this study from Bakırköy Maternity and Pediatrics Training and Research Hospital (29.4.2009/219).

Informed Consent: Written informed consent was obtained from patients and parents of patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.U.A., H.O.; Design - S.U.A.; Supervision - S.U.A, S.G.; Funding - S.U.A., S.G., T.K.; Materials - S.U.A, H.O.; Data Collection and/or Processing - S.U.A, S.G.; Analysis and/or Interpretation - S.U.A., E.A.; Literature Review - S.U.A., T.K.; Writer - S.U.A.; Critical Review - H.O., S.E.A.; Other - T. K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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 edt New York, NY: Springer-Verlag, Inc; 2006.p.78. [CrossRef]
2. Fridovich-Keil J, Walter. Galactosemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D.The metabolic and molecular bases of iInherited disease. 8th ed. New York, NY: McGrawHill Medical Publishing Division; 2008.p.72.
3. Bosch AM. Classical galactosaemia revisited. J Inherit Metab Dis 2006; 29: 516-25. [CrossRef]
4. Bennett MJ. Galactosemia diagnosis gets an upgrade. Clin Chem 2010; 56: 690-2. [CrossRef]
5. Tokatlı A. Galaktozemi taraması. Katkı Pediatri Dergisi 2000; 21: 214-23.
6. Öztürk Y, Erdur B, Tokgöz Y. Klasik galaktozemili olgularda klinik özellikler. Türkiye Klinikleri J Pediatr 2010; 19: 16-9.
7. Fedakar A, Dursun F, Ceyhan İ, Yıldız M, Ergüven M. Galaktozemi. Göztepe Tıp Dergisi 2004; 19: 248-250.
8. 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.
9. Henderson H, Leisegang F, Brown R, Eley B. The clinical and molecular spectrum of galactosemia in patients from the Cape Town region of South Africa. BMC Pediatr 2002; 2: 2-7. [CrossRef]
10. Krantz S. Early diagnosis of inherited metabolic disorders towards improving outcome: the controversial issue of galactosemia. Eur J Pediatr 2003; 162: 50-3. [CrossRef]
11. Shah V, Friedman S, Moore AM, Platt BA, Feigenbaum ASJ. Selective screening for neonatal galactosemia: an alternative approach. Acta Pediatr 2000; 948-9.
12. Schweitzer S. Newborn mass screening for galactosemia. Eur J Pediatr 1995; 154: 37-9. [CrossRef]
13. Waggoner DD, Buist NRM, Donnell GN. Long-term prognosis in galactosaemia result of a survey of 350 cases. J Inher Metab Dis 1990; 13: 802-18. [CrossRef]
14. Coşkun T, Erkul E, Seyrantepe V, Ozgüç M, Tokatlı A, Ozalp I. Mutational analysis of Turkish galactosaemia patients. J Inher Metab Dis 1995; 18: 368. [CrossRef]
15. Widger J, O'Toole J, Geoghegan O, O'Keefe M, Manning R. Diet and visually significant cataracts in galactosaemia: is regular follow up necessary? J Inherit Metab Dis 2010; 33: 129-32. [CrossRef]
16. Dobrowolski SF, Banas RA, Suzow JG, Berkley M, Naylor EW. Analysis of common mutations in the galactose-1-phosphate uridyltransferase gene. J Mol Diag 2003; 5: 42-7. [CrossRef]
17. Seyrantepe V, Ozgüç M, Coşkun T, Ozalp I, Reichardt KV. Identification of 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. [CrossRef]
18. Murphy M, Mchugh B, Tighe O, et al. Genetic basis of transferase deficient galactosaemia in Irland and the population history of the Irısh Travellers. Eur J Hum Genet 1999; 7: 549-54. [CrossRef]
19. Steven F, Richard A, Joseph G, Berkley M, Maylor E. New assays to icrease the sensitivity and specificity of newborn screening for galactosemia. J Mol Diagn 2003; 5: 42-7.
20. Shin YS, Koch HG, Köhler M, Hoffmann G, Patsoura A, Podskarbi T. Duarte-1 (Los Angeles) and Duarte-2 (Duarte) variants in Germany: two new mutations in the GALT gene which cause a GALT activity decrease by 40-50% of normal in red cells. J Inherit Metab Dis 1998; 21: 232-5. [CrossRef]
21. Gathof BS, Sommer M, Podskarbi T, et al. Characterization of two stop codon mutations in the galactose-1-phosphate uridyltransferase gene of three male galactosemic patients with severe clinical manifestation. Hum Genet 1995; 96: 721-5. [CrossRef]
22. Schuster V, Podskarbi T, Ottensmeier H, Haubner M, Shin YS. Simultaneous occurrence of various mutations and polymorphisms in cis and in trans of the galactose-1-phosphate uridyltransferase gene in a Turkish family with classical galactosemia. J Mol Med 1998; 76: 715-9. [CrossRef]
23. Walter JH, Collins JE, Leonard JV. Recommendations for the management of galactosaemia. UK Galactosaemia Steering Group. Arch Dis Child 1999; 80: 93-6. [CrossRef]
24. Panis B, Gerver WJ, Rubio-Gozalbo ME. Growth in classical galactosemia patients. Eur J Pediatr 2007; 166: 443-6. [CrossRef]
25. Shield JPH, Wadsworth EJK, MacDonald A, et al. The relationship of genotype to cognitive outcome in galactosaemia. Arch Dis Child 2000; 83: 248-50. [CrossRef]
26. Cleary MA, Heptinstall LE, Wraith JE, Walter JH. Galactosaemia: relationship of IQ to biochemical control and genotype. J Inher Metab Dis 1995; 18: 151-2. [CrossRef]
27. Porta F, Pagliardini S, Pagliardini V, Ponzone A, Spada M. Newborn screening for galactosemia: a 30-year single center experience. World J Pediatr 2015; 11: 160-4. [CrossRef]
28. Berry GT. Galactosemia: when is it a newborn screening emergency? Mol Genet Metab 2012; 106: 7-11. [CrossRef]
29. Pollak A, Kasper DC. Austrian Newborn Screening Program: a perspective of five decades. J Perinat Med 2014; 42: 151-8. [CrossRef]
30. Camelo Junior JS, Fernandes MI, Jorge SM, et al. Newborn screening for galactosemia: a health economics evaluation. Cad Saude Publica 2011; 27: 666-76. [CrossRef]