대한 유전성 대사 질환 : 2020;20(1):14~23

증 례

갈락토스 혈증: 한국인 갈락토스 환자 증례보고와 문헌 고찰

충남대학교 의과대학 부속병원 소아청소년과[1], 미국 보스톤 하바드 대학 부속 아동병원 유전학과[2]

유승우[1] · 강미현[1] · 이용욱[1] · 장미영[1] · Harvey L. Levy[2] · 김숙자[1]

Galactosemia: A Korean Patient and Literature Review

Seung Woo Yu[1], Mi Hyeon Gang[1], Yong Wook Lee[1]
Mea Young Chang[1], Harvey L. Levy[2], Sook Za Kim[1]

Department of Pediatrics[1], Chungnam National University Hospital, College of Medicine, Chungnam National University, Daejeon, Korea
Division of Genetics and Genomics[2], Children's Hospital, Harvard Medical School, Boston USA

Classic galactosemia is a rare genetic disorder in Korea and the mutation spectrum in Koreans differs from that of Caucasians and non-Caucasian Americans. Classic galactosemia is considered a metabolic complication that is preventable by early detection via newborn screening and dietary treatment. In this most recent case of Korean galactosemia, the patient showed early initiation of clinical symptoms, which manifested during the neonatal period. The patient achieved normalization via diet management to correct metabolic complications. In addition, we assessed the characteristics of mutations in 25 Korean galactosemia cases via a literature review of studies associated with classic galactosemia.

Key words: Galactosemia, Galactose-1-Phosphate Uridyl-Transferase deficiency, GALT deficiency, Galactitol, Cataracts

Introduction

Classic galactosemia is a rare inherited autosomal recessive genetic metabolic disorder that compromises galactose metabolism due to galactose-1-phosphate uridyltransferase (GALT) enzyme deficiency[1)]. Based on residual erythrocyte GALT activity and the levels of galactose metabolites, such as erythrocyte galactose-1-phosphate and urine galactitol, GALT deficiency galactosemia may be divided into three clinical/biochemical phenotypes: classic galactosemia, clinical variant galactosemia, and biochemical variant galactosemia[2)].

The most common mutations seen in Caucasian and African American populations are p.Q188R and p.S135L, respectively[3-5)]. However, neither of these mutations has been detected to date in Asian populations. Similarly, mutations that are specific to Japanese patients, such as p.V85_N97 delinsRfsX8, p.W249X, and p.R231H, have not been observed in Caucasians or African Americans, providing further evidence for genetic heterogeneity among ethnic groups[1,6,7)].

Compared to the rest of the world, the frequency of classic galactosemia in Korea and other Asian populations is very rare[2)]. Between 1999

책임저자: 김숙자, 대전 중구 문화로 282
충남대학교 부속병원 소아청소년과
Tel: 043)216-8280, Fax: 043)215-8288
E-mail: kimgenee@naver.com

and 2018, 25 patients with classic galactosemia have been reported in Korea[8-11]. The ethnic diversity of GALT mutations is emphasized by the distinct mutations in Asians as opposed to those in Caucasians and African Americans[8].

The purpose of this report is to elucidate the clinical and molecular characteristics of Korean classic galactosemia. The current study describes the most recent case of mild classic galactosemia in a Korean patient and reviews all previously reported Korean cases.

1. Patients

A 26-day-old baby boy presenting with abnormal results on newborn screening for galactosemia, and a review of 25 patients from previously reported cases in Korea.

2. Methods

Clinical information and results from laboratory and molecular tests were evaluated.

The newborn screening test (NST) and total galactose and galactose-1-phosphate analysis were performed using a blood sample from the heel capillary and a dried blood spot sample.

For the newborn found to be positive for galactosemia in screening tests, a confirmatory test was performed via the detection of elevated total galactose and galactose-1-phosphate levels, reduced GALT enzyme activity, and elevated galactitol levels.

Galactose and galactose-1-phosphate were measured via fluorometric detection[12]. GALT activity in red blood cells (RBCs) was measured using an AutoDELFIA® immunoassay[13]. Urine galactitol was measured via gas chromatography/mass spectrometry[14]. Sanger sequencing was used to identify GALT gene mutations[15].

Case report

A 26-day-old baby boy presented with abnormal results in the NST for galactosemia, as well as increased levels of multiple amino acids, including glycine, methionine, phenylalanine, tyrosine, ornithine, citrulline, and arginine, detected via metabolic evaluation. A repeat test using a second sample yielded similar results.

The baby was the first child of a 33-year-old woman. The parents were non-consanguineous. The pregnancy was complicated by premature rupture of membranes lasting 72 hours, hospitalization, and a 5-day antibiotic treatment. The baby displayed vertex presentation, and was delivered by C-section at 38+2 weeks of gestation due to failure of induction. The birth weight was 3,300 g. The mother was given one dose of dexamethasone, iron, folic acid, omega 3, and lactobacilli during pregnancy, and her blood test showed an elevation of C-reactive protein levels the day before the baby's admission.

There was no history of perinatal asphyxia, and examination of the newborn revealed no obvious congenital anomalies. Following his birth, the baby was treated with prophylactic antibiotics for 3 days, and the initial septic work-up was negative. He was fed both breast milk and formula, and he did not vomit. At 7 days of age, the baby developd jaundice, and his face became puffy.

The baby's growth parameters determined via physical examination were as follows: body weight, 3,770 g (50^{th}-90^{th} percentile); length, 53 cm (50^{th}-90^{th} percentile); and head circumference, 35.5 cm (50^{th}-90^{th} percentile). His vital signs were as follows: temperature, 37.8℃; heart rate, 153 beats/min; respiratory rate, 56 breaths/min;

and blood pressure, 70/42 mm Hg.

The baby was alert, displayed good physical activity, cried vigorously, and had normal muscle tone. His skin color was icteric, and localized edema was noticeable on both legs and feet. The head showed normocephaly, and the neck showed symmetry; the fontanelle was flat, open, and 1×1 cm in size.

Ophthalmologic examination showed icteric sclera without cataract.

The thoracic cavity was symmetric, and breathing was clear. Heart examination revealed a regular sinus rhythm without murmur. The abdomen was flat and soft. The liver was soft and palpable 2 cm below the right costal margin.

Genital examination showed an undescended right testis with mild hydrocele. The anus was patent. There was no sacral dimple. Neonatal reflexes, including Moro, sucking, tonic neck, and startled response, were all normal; urine output was good, and stool color was normal.

Family history: Both parents are of Korean descent, are non-consanguineous, and have no family history of cataract or liver or kidney disease (Fig. 1).

Results

1. Clinical course

The baby was admitted to our hospital at 14 days of age. Laboratory findings revealed thrombocytopenia (49k, 27k, 23k), obtained on different days, and soy formula was introduced. On day 2 after admission, platelet transfusion (50 cc) was performed. The urine tested negative for reducing sugar. The next day, he developed a fever and became restless, and frequent loose stools were observed. The white blood cell (WBC) count increased from 5,800 to 32,700. Antibiotics (amikacin and ampicillin) were started. On day 2 after admission, edema of the face and extremities was evident, and the blood urea nitrogen (BUN) level was elevated. The antibiotics were changed to cefotaxime and ampicillin. Although the fever subsided, procalcitonin levels were elevated. The baby was transferred to the university hospital. On day 4 after admission, edema of the face and extremities was accompanied by elevation of BUN from 15.4 mg/dL to 32.1 mg/dL. On day 5 after admission, the following were observed: ABGA: pH 7.38 (7.35-7.45); PCO_2, 37 (32.0-45.0 mmHg); PO_2, 61 (75-100.0 mmHg); BE, -2.9 (-3.4-1.4 mmol/L); HCO_3, 21.9 (19-24 mmol/L); SPO_2, 90 (96-97%); O_2 Con, 11.0 (17.5-23.0 mL/dL); and TCO_2, 23 (19-24 mmol/L) (Table 1).

Ultrasonography of the abdomen, taken on admission to the university hospital, revealed mild pelvic dilation and a small amount of ascites.

On day 9 following admission, the baby tested positive for influenza A virus subtype H3.

Ophthalmologic examination revealed normal findings and no cataract.

Metabolic evaluation showed a milder form of classic galactosemia.

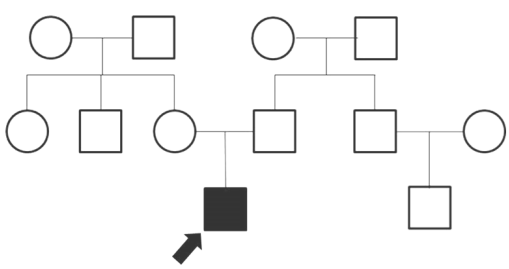

Fig. 1. Family pedigree.

2. Laboratory tests

Initial laboratory evaluation showed the following: Platelet (PLT), 23,000; Lact, 1.34 mmol/L; Blood ammonia (NH_3), 160 μg/dL; Na, 133 mmol/L; K, 4.9 mmol/L; Cl, 110 mmol/L; AST, 43 IU/L; ALT, 25 IU/L; alkaline phosphatase (ALP), 410 IU/L; total protein, 4.4 g/dL; albumin, 2.9 mg/dL; glucose, 78 mg/dL; Cholesterol, 60 mg/dL; triglyceride (TG), 36 mg/dL; BUN, 15.4 mg/dL; creatinine, 0.45 mg/dL; uric acid, 3.0 mg/dL; CPK, 195 U/L; P, 4.3 mg/dL; Ca, 9.9 mg/dL; Mg, 1.9 mg/dL; CRP, 0.70 mg/dL; LDH, 476 U/L; RBCs in urine, 5–10; and occult blood in urine, 2+.

3. Biochemical and metabolic evaluation

CBC showed thrombocytopenia (49k), while serum ferritin was 1,914.2. Total bilirubin and direct bilirubin were 16.36 and 8.3 mg/dL, respectively.

For urine, Benedict's test and Clinitest were strongly positive for reducing substances. Total galactose was 99.7 (reference <12.4 mg/dL); galactose-1-phosphate, 19.1 (reference <12.4 mg/dL); and urine galactitol, 12,283.7 (reference <90 μmol/mmol creatinine) (Table 2, Fig. 2).

Plasma amino acid analysis (μmol/L) showed that the levels of glycine (688), methionine (651.7), phenylalanine (192.9), tyrosine (706.9), ornithine (352.9), and arginine (290) were elevated (Table 3, 4, Fig. 3).

Urine organic acid analysis indicated tyrosyluria (4-OH-phenylacetic acid, 146.6; 4-OH-phenylpyruvic acid, 918; and 4-OH-phenyllactic acid 3,213 mmol/mmol creatinine). Urine amino acid analysis showed generalized aminoaciduria (Table 5, 6, Fig. 4).

Table 1. Bilirubin, Platelet, and Ferritine

	2018. 12.18	2018. 12.19 (After soy formula)	2018. 12.20	2018. 12.22	2019. 01.09	2019. 02.12	2019. 04.12	2019. 05.26
Total bil/direct bil	16.36/8.3	15.89/8.64	16/8.63	8.86	2.19	0.56	0.31	0.26
PLT	49	27	23 (Platelet transfusion)	180	392	409	437	342
Ferritine	1914.2			1289.70	721.60	233.33		

Table 2. Galactose

Metabolic Test results	Reference Range	2018. 12.18	2018. 12.19	2018. 12.21	2019. 01.02	2019. 01.09	2019. 02.12	2019. 04.12	2019. 05.26	2019. 07.07
Galactose	12.4 mg/dL (≤)	99.7	13.8	13.8		4.3	3.9	0.3	0.7	
Galactose-1-phosphate	12.4 mg/dL (≤)	19.1	7.4	7.4		0.1	1.2	0.1	0.1	
Benedict/Clinitest	Negative	2++/3++	Negative	Negative	Negative	Negative	Negative	Negative	Negative	
Galactitol	<1 Year 0-94.7	12,283.7	3535		79.8			259.3	143.99	
Galactose-1-uridyltransferase (GALT)	12.96-26.46 umol/hr/g Hb	4.55		2.4						
UDP-Gal-4-Epimerase (GALE)	3.30-6.04 umol/hr/g Hb	15.10								
Galactokinase (GALK)	<1 month 80-120 umol/hr/g Hb	19.4								

The galactose metabolic enzyme test revealed the following: GALT, 4.55 μmol/h/gHb (reference, 12.96–26.46 μmol/h/gHb); UDP–Gal–4–epimerase, 15.10 (reference, 3.30–6.04 umol/hr/g Hb); and galactokinase, 19.4 (reference, 80–120 umol/hr/g Hb).

4. GALT gene mutation analysis

Heterozygous LP variants: p.A276N and p.Q346P were detected in GALT (Fig. 5).

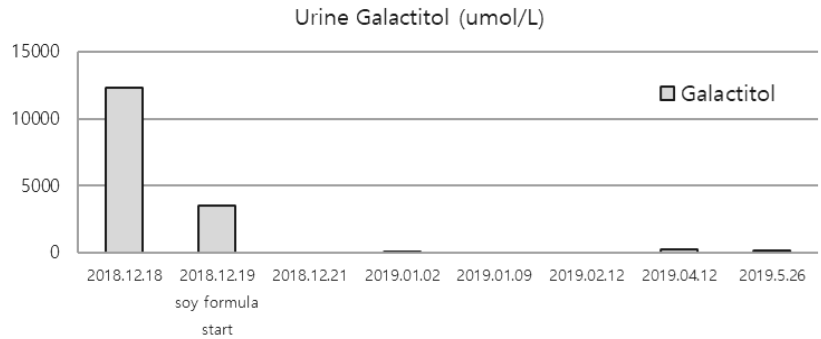

Fig. 2. Urine galactitol.

Table 3. Newborn screening using Tendem Mass Spectrometry

	ref. (μmol/L)	2018.12.18	2018.12.18
Gly	32.9–500		688.00
Met	3.29–70.00	394.99/600	651.74
His	0.00–200.00		257.91
Phe	19.74–139.30	571.17/586.45	192.95
Tyr	13.16–298.70	1150.20/918.00	706.90
Orn	7.24–180.00	381.46/792.97	352.93
Cit	1.32–50.00	89.42/160.13	170.72
Arg	0.00–50.00	229.87/303.77	290.55

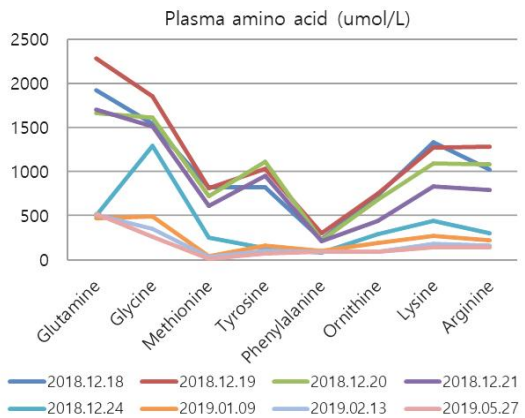

Fig. 3. Plasma amino acid.

Table 4. Plasma Amino Acid

Amino acid (umol/L)	2018. 12.18	2018.12.19 (After soy formula)	2018. 12.19 (On soy formula)	2018. 12.21 (On soy formula)	2018. 12.24 (On soy formula)	2019. 01.09 (On soy formula)	2019. 02.13 (On soy formula)	2019. 05.27 (On soy formula)	2019. 07.07 (On soy formula)
Glutamine	1,934	2,296	1,674	1,711	518	484	528	534	
Glycine	1,552	1,866	1,621	1,522	1,307	501	365	276	
Methionine	831	826	730	622	260	54	41	26	
Tyrosine	829	1,046	1,122	965	142	171	113	81	
Phenylalanine	240	313	234	221	94	114	104	102	
Ornithine	742	759	690	454	302	200	102	99	
Lysine	1,345	1,285	1,099	840	449	283	193	154	
Arginine	1,030	1,290	1,097	801	318	229	177	157	

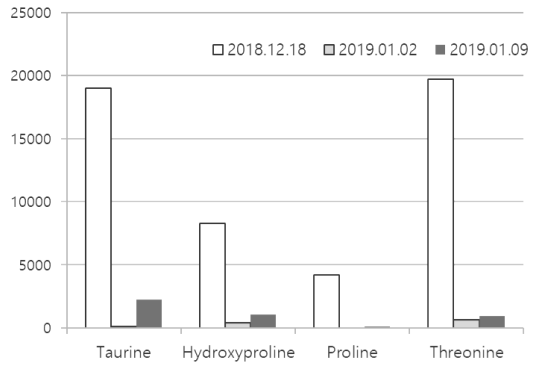

Fig. 4. Urine amino acid analysis.

Discussion

Classic galactosemia is caused by a deficiency of GALT. This disease is very rare in Korea com-

Table 6. Urine Organic Acid

	2018. 12.18	2018. 12.23	2019. 01.02	2019. 01.09
4-OH-phenylacetic	146.6	13.2	70.8	82.5
4-OH-phenylpyruvic	918	3.7	12.6	11.3
4-OH-phenyllactic	3,213	29.5	69	7.5

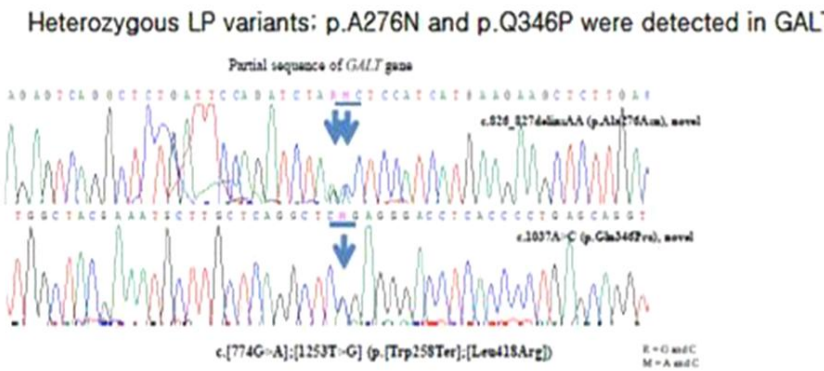

Fig. 5. Heterozygous LP variants: p.A276N and p.Q346P were detected in GALT.

Table. 5 Urine Amino Acid Analysis

Amino acid (umol/g Cr)	2018/12/18	2019/01/02	2019/01/09	2019/02/13	2019/07/07	0-1m
Taurine	1,8977	145	2,289	2,480		71-1,998
Hydroxyproline	8,319	402	1,064	695		177-2,829
Proline	4,202		142	296		186-1,883
Threonine	19,703	642	943	507		177-1,220
Serine	45,157	1,036	2,404	1,643		707-2,493
Glutamine	52,762	356	755	963		460-1,812
Glycine	56,718	2,985	4,324	4,057		2,502-9,698
Alanine	3,350	552	1,174	980		663-2,157
Citrulline	11,475		163	80		0-97
Valine	943		267	225		27-230
Cystine	2,310		331	156		106-345
Methionine	3,585		173	96		62-239
Leucine	869					27-221
Tyrosine	23,528	347	989	678		53-486
Phenylalanine	2,956	149	301	260		35-283
Ornithine	7,662	126	375	559		0-168
Lysine	31,933	500	1,659	1,309		194-1,512
Histidine	36,318	511	1,692	226		707-2,608
Arginine	3,065	53	171	116		0-124
Cystathionine	3,528	0	0	0		0

Table 7. Reported Cases of Classic Galactosemia

Year/Age/Sex	Galactosemia/ Galactose-1-phosphate (mg/dL)	Enzymes (GALT/GALE, GALK) (mol/h/gHb)	Total bilirubin/direct bilirubin (mg/dL), chemistry	Mutation spectrum of GALT
2008/11 d/M	50	14.9/34.5/1.9 (20-35/19-35/1.2-1.8)	TB/DB 27.3/2.2, PT/PTT (sec) 43.2/71.4, AST/ALT (IU/L) 73/54, protein/albumin (g/dL) 4.4/2.5, BUN/Cr (mg/dL) 5/0.5	c.252+1G>A and c.507G>C
2002/1 mo/*		6.7 (25.7±3.6)		Duarte 2/G
2002/1 mo/*	25.2/8.19	8.6 (25.7±3.6)		Duarte 2/G
2009/**/F	18.2/1.80	28		p.Q169H, c.821-7A>G
2010/**/M	76.4	<0.8		p.D96Sfs*5, c.375-1G>C, c.82-20_82+60del
2011/**/M	29.2/9.32	9		p.R333Q, p.R333Q
2012/**/F	36.8/6.38	36.5		p.D96Sfs*5, c.821-7A>G
2014/ 24.5 mo/M		<0.1		c.286_299delGACAACGACTTCCC, c.378-1G>C
2014/ 1.8 mo/F		7.3		c.286_299delGACAACGACTTCCC, c.821-7A>G
2014/ 2.3 mo/F		6.3		c.493T>C, c.998G>A)
2014/ 1.7 mo/M		1.8		c.998G>A, c.998G>A
2014/ 1.1 mo/F		6.2		c.302C>A, c.940A>G
2014/ 2.9 mo/M		5.9		c.826_827delinsAA, c.940A>G
2014/ 3.1 mo/M		15.6		c.346C>A
2014/ 2.2 mo/F		14.5		c.602G>A
2014/ 3.1 mo/M		11.6		c.769C>A
2014/ 2.9 mo/F		16.4		c.1087G>A
2014/ 3 mo/F		12.5		c.940A>G
2014/ 3.5 mo/F		12.6		c.940A>G
2014/ 5.2 mo/M		16.1		c.940A>G
2011/7 d/F	13.5/62.8	0.1	AST/ALT 34/12, jaundice	c.252+1G>Aa,c.507G>C (p.Gln169His)
2011/11 d/M	68.9/1.6	0.3	AST/ALT 48/48, jaundice	c.252+1G>Aa,c.1087G>A (p.Glu363Lys)a
2010/11 d/F	50/10.4	0.8	AST/ALT 680/135, jaundice	c.252+1G>Aa,c.507G>C (p.Gln169His)
2003/2 mo/F	18.3/7.99	4.1/44.9/94.7	TB 1.4, AST/ALT 41/54	Duarte variant/classical galactosemia
2018/26 d/M	99.7/19.1	4.55	TB/DB 16.36/8.3, AST/ALT 43/25	p.A276N, p.Q346P

*sex not clear in the literature, **age not described in the report.

pared with galactosemia caused by GALT deficiency in Caucasians and African Americans. The total number of reported classic galactosemia cases in Korea thus far is 25 *(reviewed in Table 7). Galactosemia has mostly been detected via newborn screening and clinical testing, and follow-up data are limited. In most cases, galactosemia was present during the neonatal period following jaundice, hepatomegaly, lactation intolerance, hypoglycemia, and renal tubular insufficiency.

The patient with galactosemia reported herein presented with jaundice, including direct and indirect hyperbilirubinemia and thrombocytopenia. The levels of galactose, galactose-1-phosphate, galactitol, and multiple amino acids were elevated. Following a galactose-restricted diet, jaundice was cured in 3 weeks, and urine galactitol decreased to near-reference levels.

Elevated plasma amino acid levels and tyrosyluria normalized 1 week after galactose restriction and with 3-week dietary management. Ferritin was normalized 2 months after galactose restriction.

The initial symptom of GALT deficiency is failure to thrive, leading to developmental insufficiency[16]. Vomiting, diarrhea, and other symptoms mostly appear a few days after feeding. In most children, jaundice develops within 1 week after birth[17]. Abnormal liver function and hepatomegaly appear, which, if left untreated, may lead to cirrhosis. Reasons for the presence of ascites without portal hypertension or hypoalbuminemia remain unclear. Fat accumulation and inflammatory changes, which occur in the liver at a histological level, may progress to bile stagnation, causing portal fibrosis. This cannot be distinguished from terminal liver disease. Cataracts appearing as puncture lesions in the nucleus of the fetal lens a few days after birth can only be diagnosed via a slit lamp test. In addition, drowsiness and hypotension may be observed, and mental retardation may be seen a few months after birth. In addition, the probability of death from *Escherichia coli* sepsis increases with the severity of the clinical course [18]. Therefore, galactosemia should be suspected if hyperbilirubinemia or *E. coli* sepsis is detected.

In cases where newborn screening detects galactosemia, the first step should be the administration of a urine Clinitest and Glucostix test. If positive results are obtained, lactose restriction is required until a confirmatory test for free galactose, galactose-1-phospate, and galactose enzymes in RBCs, and galactitol in urine is performed. The portosystemic shunt, another source of galactose, should be examined by imaging studies, sonography, or MRI.

In classic galactosemia, the preferred treatment for metabolic disorders is lactose restriction followed by supplementation with soy formula. Liver dysfunction; galactosuria; and proteinuria, including aminoaciduria, as well as nausea and vomiting, will all be resolved following soy formula feeding. However, our patient responded rapidly and positively to classic galactosemia management regime, suggesting the unclassified variant may confer compromised GALT activity that is perhaps too localized to dampen metabolic insult associated with classic galactosemia.

Metabolic follow-up includes the evaluation of galactose-1-phospate in RBCs. The galactose-1-phospate level in well-controlled galactosemia is below 100 μmol/L RBCs (reference level, 50 μmol/L RBCs). A finding of high galactose in galactose-restricted patients might be caused by endogenous galactose in the body[19].

Classic galactosemia (G/G) due to the lack of GALT is an autosomal recessive disorder. Classic galactosemia is a typical form of severe galactosemia found in Caucasians, and several studies have indicated Q188R and K285N to be the most commonly associated genetic mutations found in Caucasians with galactosemia[20]. Meanwhile, classic galactosemia is also expressed in a milder form in African Americans, but they do not exhibit GALT activity in the RBCs and instead show approximately 10% enzymatic activity in the liver or intestinal mucosa[5]. However, this form of the disease has not yet been reported in Korea.

In a typical galactosemia patient, early dietary modification leads to relatively normal growth, as well as normal liver and kidney function. However, some reports indicate that although a lactose-free diet improves cataract, it does not eliminate it completely. Furthermore, long-term follow-up has shown that many patients may experience developmental delays, learning disabilities, and language disorders, while others may develop growth disorders[21,22].

Despite exogenous galactose restriction, endogenous galactose production may approach 1.0-2.0 g/day[23,24]. Therefore, in the management of older children and adults, who no longer depend on milk as their primary source of energy, "self-intoxication" with galactose might be more problematic than the restriction of galactose from exogenous sources[22].

요 약

고전적 갈락토스 혈증은 한국에서 드물게 발생하는 유전 대사 질환이다. 또한 한국인의 돌연변이 스펙트럼은 코카시안과 비코카시안의 돌연변이 스펙트럼이 다르다.

한국에서 고전적 갈락토스 혈증은 임상적으로 서방국가와 유사하지만 분자적 연구에 따르면 백인, 아프리카인, 미국인, 일본인 및 한국인에게 고유한 돌연변이가 나타났다. 고전적인 갈락토스 혈증은 신생아 스크리닝 검사로 조기 발견하여 식이요법을 할 경우 대사질환으로 인한 합병증이 예방될 수 있다고 생각되어 왔다.

한국의 고전적 갈락토스 혈증의 가장 최근의 사례에서 신생아 시기에 임상 증상이 시작되었다. 식이 치료를 통하여 합병증이 교정되어 정상화 되었다. 추가로 저자들은 25명의 고전적 갈락토스 혈증을 가진 돌연변이의 특징을 리뷰했다.

References

1) Bosch AM. Classical galactosemia revisited. J Inherit Metab Dis 2006;29:516-25.
2) Berry GT. Classic galactosemia and clinical variant galactosemia. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. 2000 Feb 4 [updated 2017 Mar 9].
3) Gort L, Boleda MD, Tyfield L, Vilarinho L, Rivera I, Cardoso ML, et al. Mutational spectrum of classical galactosaemia in Spain and Portugal. J Inherit Metab Dis 2006;29:739-42.
4) Tyfield L, Reichardt J, Fridovich-Keil J, Croke DT, Elsas LJ, Strobl W, et al. Classical galactosemia and mutations at the galactose-1-phosphate uridyl transferase (GALT) gene. Hum Mutat. 1999;13:417-30.
5) Lai K, Langley SD, Singh RH, Dembure PP, Hjelm LN, Elsa, LJ. A prevalent mutation for galactosemia among black Americans. J Pediatr. 1996;128:89-95.
6) Hirokawa H, Okano Y, Asada M, Fujimoto A, Suyama I, Isshiki G. Molecular basis for phenotypic heterogeneity in galactosaemia: prediction of clinical phenotype from genotype in Japanese patients. Eur J Hum Genet 1999;7:757-64.
7) Ashino J, Okano Y, Suyama I, Yamazaki T, Yoshino M, Furuyama J, et al. Molecular characterization of galactosemia (type 1) mutations in Japanese. Hum Mutat 1995;6:36-43.
8) Lee BH, Cheon CK, Kim JM, Kang M, Kim JH, Yang SH, et al. Low prevalence of classical galactosemia in Korean population. J Hum Genet 2011;56:94-6.
9) Choi R, Jo KI, Ko DH, Lee DH, Song J, Jin DK, et al. Novel GALT variations and mutation spectrum in the Korean population with decreased galactose-1-phosphate uridyltransferase activity. BMC Med Genet 2014;15:94.
10) Young BS. Diagnostic algorithm of newborn screening for galactosemia. J Korean Soc Inher Metab Dis 2015;15:101-9.
11) Cheon CK, Cho MS, Ko JM, Kim GH, Yoo HW. A case of classical galactosemia caused by compound heterozygous mutations of the GALT gene. J Genet Med 2008;5:131-5.
12) Lafleur JP, Senkbeil S, Novotny J, Nys G, Bøgelund N, Rand KD, et al. Rapid and simple preparation of thiol-ene emulsion-templated monoliths and their application as enzymatic microreactors. Lab Chip 2015;15:2162-72.
13) Adam BW, Flores SR, Hou Y, Allen TW, De Jesus VR. Galactose-1-phosphate uridyltransferase dried blood spot quality control materials for newborn

screening tests. Clin Biochem 2015;48:437-42.
14) Palmieri M, Mazur A, Berry GT, Ning C, Wehrli S, Yager C, et al. Urine and plasma galactitol in patients with galactose-1-phosphate uridyltransferase deficiency galactosemia. Metabolism 1999;48:1294-302.
15) Sanger F, Coulson AR. A rapid method for determining sequences in DNA by primed synthesis with DNA polymerase. J Mol Biol 1975;94:441-8.
16) Holton JB, Walter JH, Tyfield LA. Galactosemia. In: Stansbury J, Wyngarden J, Fredrickson D, Goldstein JL, Brown US, editors. 8th ed. New York: McGraw Hill, 1992;1553-85.
17) Segal S, Berry GT. Disorder of galactose metabolism. In: Stansbury J, Wyngarden J, Fredrickson D, Goldstein JL, Brown US, editors. 7th ed. New York: McGraw Hill, 1990;967-90.
18) Levy HL, Sepe SJ, Shih VE, Vawter GF, Klein JO. Sepsis due to Escherichia coli in neonates with galactosemia. N Engl J Med 1977;297:823-5.
19) Park IS, Cho HJ, Lee DH, Song JH. Galactosemia detected by neonatal screening test. J Korean Pediatr Soc 2003;46:440-6.
20) Jama M, Nelson L, Mao R, Lyon E. Simultaneous Amplification, Detection, and Analysis of Common Mutations in the Galactose-1-Phosphate Uridyl Transferase Gene. J Mol Diagn 2007;9:618-23.
21) Waggoner DD, Buist NRM, Donnell GN. Long-term prognosis in galactosemia: Results of a survey of 350 cases. J Inherit Metab Dis 1999;13:802.
22) Bosch AM. Classic galactosemia: dietary dilemmas. J Inherit Metab Dis 2011;34:257-60.
23) Berry GT, Leslie N, Reynolds R, Yager CT, Segal S. Evidence for alternate galactose oxidation in a patient with deletion of the galactose-1-phosphate uridyltransferase gene. Mol Genet Metab 2001;72:316-21.
24) Schadewaldt P, Hammen H-W, Stolpmann S, Kamalanathan L, Wendel U. Galactonate determination in urine by stable isotope dilution gas chromatography-mass spectrometry. J Chromatogr B 2004;801:249-55.