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Unusual Presentation of Classical Galactosemia: A Case Report of Iranian Experience

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ABSTRACT

Galactosemia is a rare autosomal recessive metabolic disorder with four main types, and classic galactosemia is the most prevalent. These patients have galactose-1-phosphate-uridyltransferase deficiency. We report on a case of an infant who was admitted with poor feeding, lethargy, and poor weight gain. Based on the clinical symptoms and laboratory findings, the patient was considered to have a metabolic disorder. The patient had unusual presentations such as macrocytic anemia requiring blood transfusions, repeatedly metabolic acidosis requiring bicarbonate therapy and failure to thrive in addition to neurodevelopmental delay which led the authors to different diagnoses and suspect to mitochondrial disorders. Finally, in one of the assessments before blood transfusion, a high galactose-1 phosphate was detected, and galactose-free diet was started which led to neurologic and physical of the child. The whole-exome sequencing (WES) also revealed a likely pathogenic homozygous mutation in *GALT* (c.794 C>G, p. Pro265Arg) confirming the diagnosis of classic galactosemia. In Iran, global neonatal metabolic screening is not done for galactosemia which results in late diagnosis of the affected patients. So, we suggest adding galactosemia to neonatal metabolic screening in Iran.

1 | Introduction

Inborn errors of metabolism (IEM), also known as inherited metabolic disorders, are a heterogeneous group of congenitally inherited disorders of enzyme activities consisting of more than 500 disorders and an approximate incidence of 1 per 1000 live births [1–3]. In 1902, Archibald Garrod described the first IEM [4]. IEM are caused by mutations in genes encoding enzymes that are involved in energy production or the synthesis or degradation of various substances leading to a block in a metabolic pathway and subsequently body's decreased ability of synthesizing essential compounds or accumulation of toxic substances interfering with normal function [1, 5]. IEM most commonly present with neurological manifestations, weight loss, growth failure, and jaundice [2, 6]. Based on the affected substance, IEM are classified into various groups [5].

Inborn errors of galactose metabolism, or galactosemias, belong to hereditary disorders of carbohydrate metabolism as one of the main classifications of IEM [2, 7]. In galactosemias, accumulation of metabolites particularly galactitol as the result of defective galactose metabolism is responsible for the symptoms [7]. Metabolites responsible for the hepatic, renal, and cerebral pathogenesis remain unknown but might include galactose-1 phosphate and perhaps galactitol [6]. They typically present in the first month of life simultaneous to lactose ingestion through breast milk or standard lactose-containing formulas; however, symptoms vary from asymptomatic to severe cases with

Summary

- Classic galactosemia despite its nomenclature can present with unusual nonclassic presentation which could delay diagnosis and treatment of this curable metabolic disorder.
- So, we recommend neonatal metabolic screening for galactosemia to prevent late diagnosis and complications.

life-threatening and progressive loss of function of the ovaries and brain [2, 7–9]. Galactose is mainly metabolized by the Leloir pathway through which four major cytosolic enzymes are involved and convert β-D-galactose into glucose-1-phosphate [10]. These enzymes in order of activity consist of galactose mutarotase (GALM), galactokinase (GALK), galactose-1-phosphate uridyltransferase (GALT), and uridine diphosphate (UDP)-galactose 4′-epimerase (GALE) [10]. Mutations in genes encoding the aforementioned enzymes result in types IV, II, I, and III galactosemias, respectively [10].

Type I galactosemia, also known as classical galactosemia, is an autosomal recessive disorder and the first reported case of galactosemia as well as the most common form of it with an approximate prevalence of 1 per 16,000–60,000 live births due to underlying mutations in *GALT* gene encoding GALT enzyme [11, 12]. It typically presents in newborns' first week of life within days of milk consumption with vomiting, diarrhea, poor weight gain, jaundice, lethargy, hypotonia, seizure, hepatomegaly, or liver dysfunction and could progress to the development of cataracts, liver damage, bleeding diathesis, *Escherichia coli* sepsis, and if left undiagnosed, uncured lead to ovarian failure, pseudotumor cerebri, and cognitive impairment later in life [12–15]. Galactose restriction, primarily in the form of dairy restriction such as lactose-free formula, is the mainstay treatment for symptomatic galactosemias [16, 17]. Erythrocyte galactose 1-phospate concentration is the most common biochemical marker used to monitor treatment [6]. Also, it is recommended that the patients go under regular follow-up and monitoring for systemic complications and measurement of galactitol [18]. However, there are currently no data available to demonstrate superiority of any other marker over galactose 1-phosphate for biochemical monitoring [6].

Herein, we report a case of an infant who was admitted with poor feeding, lethargy, and poor weight gain. Based on the clinical symptoms and laboratory findings, the patient was considered to have a metabolic disorder; however, the exact type of it was not determined. As no improvement was detected in his growth and development, the patient underwent whole-exome sequencing (WES) that revealed a likely pathogenic homozygous mutation in *GALT* (c.794 C>G, p. Pro265Arg) confirming the diagnosis of type I galactosemia.

2 | Case History/Examination

The patient is a 9-month-old male infant, the third child of consanguineous parents (first cousins) born term at 37 weeks of gestation through normal vaginal delivery (NVD) with birth body weight of 2900 g, birth head circumference of 35 cm, and birth height of 49 cm. His mother mentioned a history of jaundice starting from 19 days of life till the infant was 1 month old which disappeared without the need for hospital admission. His vaccination was completed till 4 months of age. Also, he had been investigated for delayed development and poor weight gain in the last 4 months of age. The infant was brought to the Mofid Children Hospital's emergency room (ER) with poor feeding and lethargy. On physical examination, his weight was under fifth percentile line, and his head circumference and height were at 25th percentile line on the growth chart (5400 g, 44 cm and 70 cm, respectively). At admission, he had tachypnea (respiratory rate = 40/min) and tachycardia (heart rate = 140/min) with low blood pressure (80/60 mmHg). He had a blond face and moderate-to-severe dehydration. His head and neck examination were normal. The anterior fontanelle was 2 × 3 cm and mildly depressed. He had a doll face with no dysmorphology like his mother and his sclera was pale. His chest had a normal shape, and his lungs and heart sounds were normal. His abdomen was mildly protruded. The liver was palpated 3 cm below the costal margin. He did not have splenomegaly. His limbs were cachectic and hypotonic with decreased force. In the neurological exam, he was alert and awake and had normal eye contact and normal red reflex on a direct fundoscopic eye exam. He had mild head lag, truncal hypotonic and normal deep tendon reflex (DTR). He was unable to sit. A detailed laboratory analysis of the infant upon his arrival at the ER is provided in Table 1.

3 | Methods

The patient underwent the metabolic study. In the first evaluation, plasma acylcarnitine profile showed low free carnitine (C0 = 6.1, normal range: 7.7–42 μmol/L), whereas plasma amino acid profile was normal. Also, urine organic acid showed ketosis and di-carboxylic acids. In the second metabolic evaluation, plasma acylcarnitine profile again showed low free carnitine (5.54), whereas plasma amino acid profile was normal, and urine organic acid profile showed increased adipic acid (30.4 mmol/mol Cr, normal range < 5) and c6-polyols (galactitol + sorbitol). Urine sugar chromatography TLC for glucose was negative but showed a doubtful band on galactose RF.

The patient then underwent an abdominal ultrasound that was normal (liver size was 70 mm with normal echo-pattern, spleen size was 43 × 22 mm, right kidney size was 50 × 22 mm, and left kidney size was 52 × 26 mm). Echocardiography showed normal systolic function and no abnormality. Electromyography (EMG) was suspicious for myopathy process, nerve conduction velocity (NCV) was normal with no evidence of polyneuropathy. Auditory brainstem response (ABR), electroencephalogram (EEG), was also normal.

In brain MRI, cerebral hemispheres, cerebellum, and brain stem were normal; however, patchy almost symmetrically nonmyelinating regions were seen in both cerebral hemispheres with extension to the juxta cortical regions indicative of mildly delayed myelination in cerebral white matter (Figure 1).

TABLE 1 | Laboratory data of the patient at time of his arrival to ER.

Variable	Result	Normal values
WBC, cells/μL	7430	5000–19,000
Lymphocytes (%)	*48%*	20%–40%
Neutrophils (%)	*41.8%*	40%–60%
Hb, g/dL	10.4	11.4–14.1
MCV, fL	101	70–86
Plt, cells/μL	259,000	205,000–533,000
AST, IU/L	63–> 70	15–60
ALT, IU/L	49–> 180	10–40
ALP, IU/L	557	81.9–350.3
CPK, μg/L	26	10–120
BUN, mg/dL	11	5–18
Creatinine, mg/dL	0.5	0.2–0.4
Cholesterol, mg/dL	97	< 75
Triglyceride, mg/dL	208	< 75
Calcium, mg/dL	9.7	7.8–11.3
Phosphorous, mg/dL	5.3	4.8–7.4
Magnesium, mg/dL	2.3	1.7–2.2
Sodium, mEq/L	133	135–145
Potassium, mmol/L	3.7	3.4–4.7
Chloride, mEq/L	108	90–110
Ferritin, ng/mL	105	7–140
Ammonia, μg/dL	86	68–136
Lactate, mg/dL	9	4.5–19.8
PH	7.36	7.40
PCO2, mmHg	22.8	40
$HCO3^-$, mEq/L	13.1	24
BE, mEq/L	−10.6	−2 to +2
Anion Gap[Na-(cl + HCO3)], mEq/L	12	8–12
PT, second	13.5	12.5–15.2
PTT, second	29	25–35
INR, second	1	0.8–1.1
Albumin, g/dL	4.5	3.4–5.4
25 hydroxy-Vitamin D3, ng/mL	39	Sufficient > 30
GGT, U/L	57	0–50
TSH, mU/L	2	0.5–5.3
FT4, ng/dL	1	0.8–2.1
AntiTTG IgA, U/mL	0.3	0–3
IgA, mg/dL	18	4–80

(Continues)

TABLE 1 | (Continued)

Variable	Result	Normal values
U/A	SG: 1022, protein:1+, ketone: trace, WBC: 1–2, RBC: 1–2, PH:5, culture: no growth	SG:1010–1030, protein:–, ketone:–, WBC:0–1, RBC:0–1 PH:4.6–8, culture: no growth
S/E	Fat drops: negative, PH: 5, elastase activity > 720 mg/g	Fat drops: negative, PH:4.5–5.5, Elastase activity > 200 mg/g

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BE, base excess, PT, prothrombin time; BUN, blood urea nitrogen; Cl, chloride; CPK, creatine phosphokinase; dL, deciliter; fL, femtoliter; FT4, free thyroxin; GGT, gamma-glutamyl transferase; Hb, hemoglobin; HCO3, bicarbonate; IgA, immunoglobulin A; INR, international normalized ratio; IU, international units; MCV, mean corpuscular volume; mEq, *milliequivalents*; mg, milligram; mL, milliunits; mmHg, millimeter of mercury; mmol, millimol; Na, sodium; ng, nanogram; PCO2, partial pressure of carbon dioxide; Plt, platelets; PTT, partial thromboplastin time; RBC, red blood cell; S/E, stool exam; SG, specific gravity; TSH, thyroid stimulating hormone; TTG, tissue transglutaminase; U/A, urine analysis; WBC, white blood cells; μg, microgram; μL, microliter.

In this stage, several differential diagnoses were considered for the patient including B12 metabolism defects, mitochondrial disorders, Fanconi-Bickel syndrome, galactosemia and peroxisomal disorders.

The patient was discharged with mitochondrial cocktail due to hypotonia and white matter abnormality, oral and intramuscularB12, and iron and folate supplementation due to macrocytic anemia. During the next few months, he underwent several blood transfusions. He was repeatedly admitted to the hospital due to severe normal anion gap metabolic acidosis. Furthermore, no improvement in his growth nor his development was seen within the first 3 months of management. In one of his hospital admissions, when he was 1 year old, when no improvement of symptoms was observed with previous therapy and severe macrocytic anemia requiring transfusion, metabolic acidosis and neurologic symptoms persisted; further evaluation of laboratory tests revealed proteinuria, impaired liver function tests, and previous galactitol in urine organic acid profile prompted authors to investigate for two other diagnoses; Fanconi–Bickle Syndrome or galactosemia. So, WES and galactose-1-phosphate in blood samples before blood transfusion were requested. The results of requested laboratory data at this time are presented in Table 2, based on which, all mitochondrial cock tail was discontinued except carnitine. Breast milk was discontinued and soy formula plus galactose-free diet was prescribed for the patient. Several months later, his WES result revealed a likely pathogenic homozygous mutation in the *GALT* gene (c.794 C>G, p. Pro265Arg) confirming the diagnosis of type I galactosemia. WES reported no other variants so authors requested reanalysis which revealed five other heterozygote mutations besides the previous homozygote mutations in GALT gene. POLR2A gene heterozygote mutation:c.2573-3C>G which can cause autosomal-dominant neurodevelopmental disorder with hypotonia and was variant of unknown significance. MLX gene heterozygote mutation:c.418 C>T which can cause Takayaso arteritis of unknown patterns of inheritance and was a variant of unknown significance. Three other heterozygotes likely pathogenic variant mutations with an autosomal recessive pattern of inheritance in genes: PHYH: c.571del, CPE: c.1114-1G>T, OTOG: c.421-1G>A causing Refsum Disease, BDY syndrome, autosomal recessive deafness, respectively, also were detected which were unrelated to patients' symptoms and signs.

He is now 20 months old and able to sit and stand without help. His weight, head circumference, and height are, respectively, 10.5 kg, 48 cm, and 70 cm. There is no further metabolic acidosis and his galactose-1-phosphate and liver function tests (LFT) are normal. Brain MRI was normal after 1 year of treatment and he is now able to say a few words, able to sit and stand but still unable to walk. Neurologic exam revealed normal tone, force, DTR of four limbs. Normal fundoscopic exam, ABR and EMG, and NCV were requested at a follow-up visit of 1 year after therapy, but the result is pending. Galactose-1-phosphate was within the normal range with galactose restricted diet during 1 year of follow-up. GALT activity was zero in washed RBCs measured by Liquid chromatography–mass spectrometry (LC–MS/MS) requested for functional study of gene analysis. The patient had normal activity of GALK and GALE.

4 | Conclusion and Results

Diagnosis of galactosemia through newborn screening and initiation of dietary treatment in the first week of life could have beneficial effects. So, we suggest including galactosemia to neonatal metabolic screening in Iran. However, long-term brain, ovarian, and skeletal complications of galactosemia are independent of early initiation of galactose-free diet and should be assessed in the affected patients. Also, several emerging treatment options are underway; however, further studies are required to confirm their efficacy.

5 | Discussion

We introduced a 9-month-old case with lethargy, poor feeding, impaired growth, and development, who had likely pathogenic homozygous mutation in *GALT*.

These patients generally present in the early stages with vomiting, diarrhea, failure to thrive, and jaundice, and late signs include liver enlargement, *Escherichia coli* sepsis and cataract [12]. We found several reports of galactosemia and indirect hyperbilirubinemia [19]. Takci et al. reported an infant with galactosemia who was admitted for indirect hyperbilirubinemia on the seventh day of life and received intensive phototherapy for 2 days [20]. Also, our case presented a history of neonatal jaundice starting from 19 days of life.

Immediate initiation of the cornerstone treatment for type I galactosemia, that is, galactose-restricted diet, is necessary in case of suspicion in a neonate and it should not be delayed

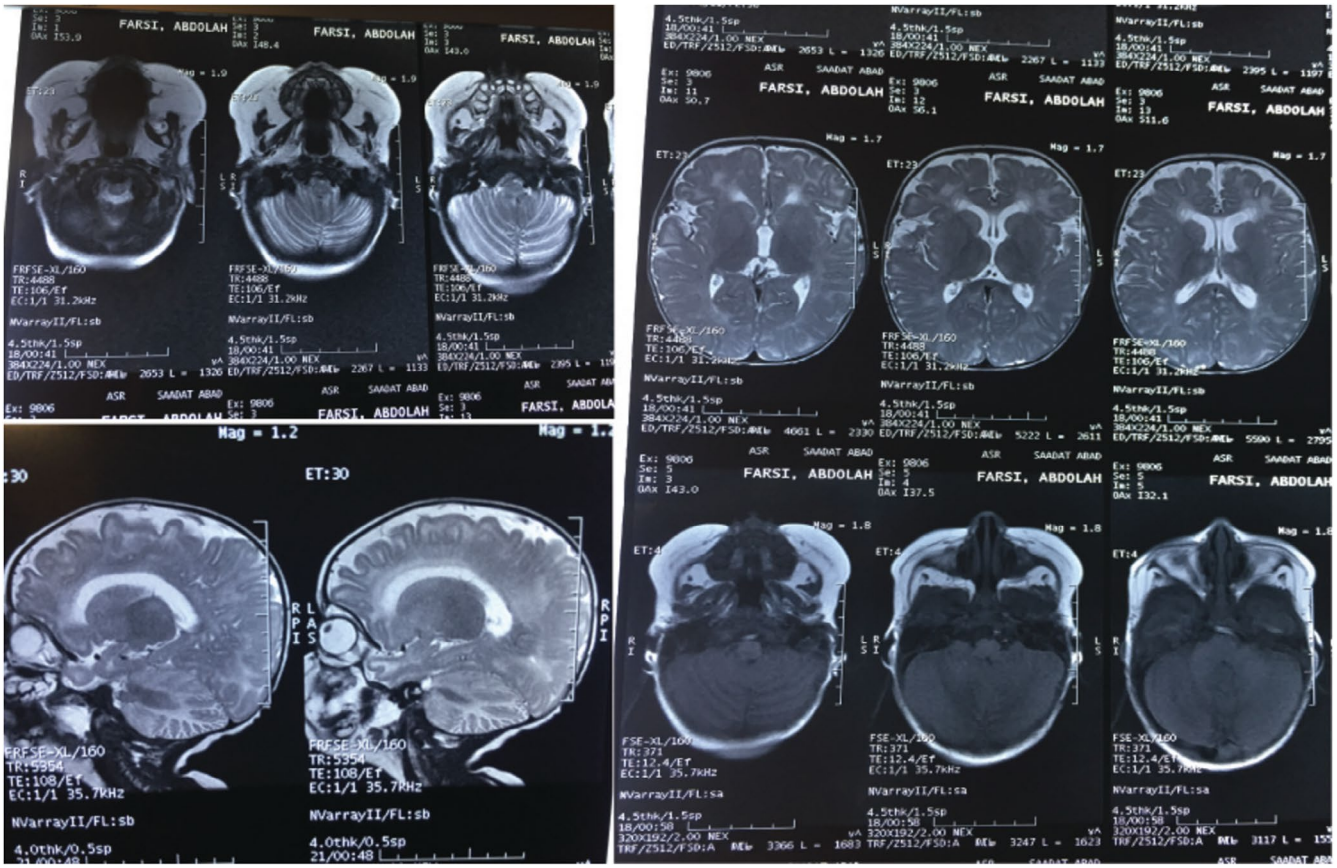

FIGURE 1 | Brain MRI of the patient at 9 months of age indicating normal cerebral hemispheres, cerebellum, and brain stem with mildly delayed myelination in cerebral white matter.

TABLE 2 | Laboratory data of the patient 3 months after initiation of management at 1 year old.

Variable	Result	Normal values
Vitamin B12, pg/mL	1890	160–1300
Folic acid, ng/mL	12.6	3.1–25
Homocysteine, μmol/L	7	6–14
Stool calprotectin: μg/g	15	Negative < 50
Urine sugar chromatography	A doubtful band on galactose RF	Normal pattern
Galactose-1-phosphate, μmol/L	275 ↑	0–50

till confirmation of the diagnosis as early and prompt treatment could lead to more favorable outcomes [21, 22]. Newborn screening for galactosemia through measuring the level of galactose and/or GALT enzyme activity has been incorporated into national programs in many countries [23–27]. This way, the affected newborns are diagnosed in advance and initiation of galactose-restricted diet in the first week of life could have beneficial effects [22]. Available literature suggests that early diagnosis and treatment with lactose-free diet in the initial 1–2 weeks of life reduce complications of liver failure and mortality [28]. In a study on 509 patients of 15 different countries by Rubio-Gozalbo et al. showed that diagnosis following newborn screening (NBS) and early initiation of galactose restriction within the first week of life were associated with a lower ratio for neonatal complications, as an enzyme activity < 1% was associated with a higher rate of acute neonatal illness [22].

Newborn screening for galactosemia is not performed in every region of Iran like our case who was not evaluated for it. In our case, the diagnosis of galactosemia was delayed till 1 year of age and he had experienced several developmental and neurological complications, which we believe could be less severe and annoying in case of early diagnosis at birth. There has been discussed about newborn screening for classic galactosemia but there is still no agreement, according to research mortality over a period of 10 years of screening for galactosemia was reduced from 4.6 to 0.3 [28]. Furthermore, a study from Iran showed that implementation galactosemia to neonatal metabolic screening lowered cost burden of disease by two third [29]. Many countries include neonatal screening for Galactosemia despite low incidence in their region such as Sweden with an estimated incidence of 1/100000 live births [28]. The overall incidence of galactosemia varies by race and ethnicity, higher among Caucasians ranging 1/16000 to 1/60000 live births [22, 28, 30]. The lowest incidence is reported from Japan which is 1/788000 live births [28]. The prevalence of classic galactosemia among populations of different ethnic backgrounds varies, its prevalence is much higher in Western populations compared to Asian populations, with prevalence rates

of 1:40,000–1:60,000 in Europe; 1:50,000 in the United States; 1:23,500–1:44,000 in the United Kingdom; 1:42,000 in Lithuania; 1:100,000 in Japan; 1:400,000 in Taiwan, China; 1:50,000 in Shenzhen, China; and 1:759,428 in Zhejiang, China [31, 32]. As discussed above global neonatal screening for galactosemia is not done in Iran. Senemar et al. published their report of screening 24,000 neonates for galactosemia in Fars province of Iran and the prevalence was 5/24,000 during 1 year period 2007–2008, so concluded that screening should be executed for all the families with a history of Galactosemia [33]. In another study by Mirzaee et al. 337,000 neonates were screened for Galactosemia again in Fars province of Iran considered the incidence rate of classic galactosemia 1/28000 live births and concluded that neonatal screening has an important role in early diagnosis and management of the disease [34]. In the first report of neonatal metabolic screening published by Shakiba et al., for 125,819 neonates NBS was done between 2018 and 2022 but galactosemia was not included [35]. Galactosemia qualifies for newborn screening as it fulfils both the traditional and new criteria for screening [30]. Thus, we recommend implementing newborn screening for galactosemia in our national program for newborn screening in Iran to diagnosis and treat the affected patients timely at birth for reducing the complications and burden of this disorder.

In our patient, dramatic physical and neurological improvement occurred in the first year of treatment with galactose-free diet but longer follow-up is needed to judge the effectiveness of galactose-restricted diet alone on the growth and development of this case which was diagnosed late at nearly first year of his life. In a cohort study done by Welsink-Karssies et al., which reported long-term follow-up data of 56 patients affected of classic galactosemia from 2007 to 2018, a large variability in clinical outcome was demonstrated and both galactose-1-phosphate, IgG N-glycan levels were not associated with long-term complications which necessitate individual and standardize evaluation of all classic galactosemia patients [36]. Despite timely initiation of a galactose-free diet at the first week of life, patients with galactosemia are reported to experience several long-term organ-specific complications including brain impairments, ovarian insufficiency in female patients, bone loss, and cataract [22, 28]. To date, the exact pathogenic mechanism of these complications has not been elucidated; however, several contributing factors have been suggested including oxidative stress, endoplasmic reticulum stress with unfolded protein response, UDP-hexose alterations, impaired glycosylation and accumulation of galactitol, galactonate, and Gal-1-P as the result of defective galactose metabolism [12].

The *GALT* gene is located on chromosome 9p13 and consists of 11 exons [22, 31, 32]. More than 300 variant mutations are reported in GALT gene which according to Human Gene Mutation Database (HGMD) c.563 A>G; p.Gln188Arg has been reported most frequently in European population [22, 32]. The c.855G>T (p.Lys285Asn) variant is common in German and Austrian populations, the c.404 C>T (p.Ser135Leu) variant is common in African American populations, c.253–2 A>G variant is common in Hispanic populations, whereas large deletions of 5 kb and 5.5 kb are common in Ashkenazi Jewish populations, in the Japanese population, the common variants include c.[940 A>G; c.-116-119delGTCA] (p.Asn314Asp) and p.R231H, no reports of a predominant type of *GALT* gene variant in the Chinese population [31, 32]. A study done by Moody M. et al., in 93 Iranian patients affected with galactosemia c.563A>G, c.855G, c.1018G>A, were the most common mutations of classic galactosemia in Iran [31]. The patient we reported had homozygote mutation of GALT gene: c.794C>G (p. Pro265Arg) which was not previously reported in HGMD. Our patient studied homozygote mutation of GALT gene: c.794C>G (p. Pro265Arg) which was not previously reported as a pathogenic variant in HGMD. This shows the necessity of global screening to help the development of gene databases for the Iranian population affected by inherited metabolic diseases such as classic galactosemia to facilitate diagnosis, treatment, and genetic counseling for patients and their families.

In addition to galactose-free diet, several novel therapeutic approaches have been explored in recent years aiming to prevent burdensome long-term complications of classical galactosemia through restoration of GALT activity (by *GALT* gene therapy, mRNA therapy, or pharmacological chaperones) or influencing the cascade of events (by inhibition of galactokinase-1 [GALK1], or aldose reductase, reduction of endoplasmic reticulum stress or oxidative stress) [37]. However, these new emerging treatment options are still underway and further studies are required to confirm their efficacy and the appropriate time of prescription. Furthermore, the affected patients should regularly exercise and receive supplementary calcium and vitamin D based on the age-specific required recommendation for improving their bone mineral density (BMD) [21, 22, 38]. Most of the affected female patients experience primary ovarian insufficiency (POI) with subsequent subfertility and should be under regular follow-up and screening by pediatric and reproductive endocrinologists for timely initiation of hormonal replacement therapy (HRT) for supplementation of hormonal insufficiency as well as ovarian tissue cryopreservation at a young age and oocyte donation for further pregnancy [22, 37, 39]. For management of neurological, cognitive, and behavioral complications that highly occur among these patients, early assessment of cognition, intellect, speech and language, behavior, and development is required for early diagnosis of any brain impairment and initiation of appropriate treatment based on available guidelines as well as several understudy approaches including transcranial alternating current stimulation (tACS) and the Babble Boot Camp (BBC), which could improve the quality of life and general performance of the affected patients [21, 22, 37].

In our patient, galactose-free diet is tolerated but several supplements are added to the diet such as Carnitine, Iron, Vitamin D, and rehabilitation therapy is done regularly but we have not any galactose-free formulas in Iran so available other than soy-based ones and long-term effect of this regimen in this patient must be evaluated in the future studies.

Author Contributions

Mohammadreza Alaee: supervision, validation, visualization. **Hedyeh Saneifard:** supervision, validation. **Marjan Shakiba:** supervision, validation. **Marjan Hanifeh:** resources. **Shirin Moarefian:** conceptualization, data curation, visualization, writing – original draft.

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Ethics Statement

Our institution does not require ethical approval to report individual cases.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data available on request from the authorsData available on request due to privacy/ethical restrictions.

References

1. R. B. Guerrero, D. Salazar, and P. Tanpaiboon, "Laboratory Diagnostic Approaches in Metabolic Disorders," *Annals of Translational Medicine* 6, no. 24 (2018): 470, https://doi.org/10.21037/atm.2018.11.05.

2. A. W. El-Hattab, "Inborn Errors of Metabolism," *Clinics in Perinatology* 42, no. 2 (2015): 413–439, https://doi.org/10.1016/j.clp.2015.02.010.

3. P. M. Campeau, C. R. Scriver, and J. J. Mitchell, "A 25-Year Longitudinal Analysis of Treatment Efficacy in Inborn Errors of Metabolism," *Molecular Genetics and Metabolism* 95, no. 1 (2008): 11–16, https://doi.org/10.1016/j.ymgme.2008.07.001.

4. A. Garrod, "The Incidence of Alkaptonuria: A Study in Chemical Individuality," *Lancet* 160, no. 4137 (1902): 1616–1620, https://doi.org/10.1016/S0140-6736(01)41972-6.

5. J. V. Leonard and A. A. M. Morris, "Diagnosis and Early Management of Inborn Errors of Metabolism Presenting Around the Time of Birth," *Acta Paediatrica* 95, no. 1 (2006): 6–14, https://doi.org/10.1111/j.1651-2227.2006.tb02172.x.

6. J. M. Saudubray and À. Garcia-Cazorla, "Inborn Errors of Metabolism Overview: Pathophysiology, Manifestations, Evaluation, and Management," *Pediatric Clinics of North America* 65, no. 2 (2018): 179–208, https://doi.org/10.1016/j.pcl.2017.11.002.

7. D. J. Timson, "The Molecular Basis of Galactosemia — Past, Present and Future," *Gene* 589, no. 2 (2016): 133–141, https://doi.org/10.1016/j.gene.2015.06.077.

8. I. Timmers, H. Zhang, M. Bastiani, B. M. Jansma, A. Roebroeck, and M. E. Rubio-Gozalbo, "White Matter Microstructure Pathology in Classic Galactosemia Revealed by Neurite Orientation Dispersion and Density Imaging," *Journal of Inherited Metabolic Disease* 38, no. 2 (2015): 295–304, https://doi.org/10.1007/s10545-014-9780-x.

9. N. L. Potter, Y. Nievergelt, and L. D. Shriberg, "Motor and Speech Disorders in Classic Galactosemia," in *JIMD Reports*, vol. 11, ed. J. Zschocke, K. M. Gibson, G. Brown, E. Morava, and V. Peters (Springer, 2013), 31–41, https://doi.org/10.1007/8904_2013_219.

10. F. Conte, N. van Buuringen, N. C. Voermans, and D. J. Lefeber, "Galactose in Human Metabolism, Glycosylation and Congenital Metabolic Diseases: Time for a Closer Look," *Biochimica et Biophysica Acta (BBA) - General Subjects* 1865, no. 8 (2021): 129898, https://doi.org/10.1016/j.bbagen.2021.129898.

11. A. Von Reuss, "Zuckerausscheidung im Säuglingsalter," *Wiener Medizinische Wochenschrift (1946)* 58 (1908): 799–801.

12. A. I. Coelho, M. E. Rubio-Gozalbo, J. B. Vicente, and I. Rivera, "Sweet and Sour: An Update on Classic Galactosemia," *Journal of Inherited Metabolic Disease* 40, no. 3 (2017): 325–342, https://doi.org/10.1007/s10545-017-0029-3.

13. N. Karadag, A. Zenciroglu, F. Eminoglu, et al., "Literature Review and Outcome of Classic Galactosemia Diagnosed in the Neonatal Period," *Clinical Laboratory* 59, no. 9–10 (2013): 1139–1146, https://doi.org/10.7754/Clin.Lab.2013.121235.

14. V. Lewis, F. Welch, F. Cherry, E. Flood, and M. Marble, "Galactosemia: Clinical Features, Diagnosis and Management. A Case Report," *Journal of the Louisiana State Medical Society* 147, no. 6 (1995): 262–265.

15. G. T. Berry, "Galactosemia: When Is It a Newborn Screening Emergency?," *Molecular Genetics and Metabolism* 106, no. 1 (2012): 7–11, https://doi.org/10.1016/j.ymgme.2012.03.007.

16. G. T. Berry, *Classic Galactosemia and Clinical Variant Galactosemia* (University of Washington, 2021), accessed September 5, 2023, https://europepmc.org/article/NBK/nbk1518.

17. A. M. Bosch, "Classical Galactosaemia Revisited," *Journal of Inherited Metabolic Disease* 29, no. 4 (2006): 516–525, https://doi.org/10.1007/s10545-006-0382-0.

18. E. Los and G. A. Ford, *Galactose-1-Phosphate Uridyltransferase Deficiency* (StatPearls Publishing, 2023), http://europepmc.org/books/NBK441957.

19. Z. Kavehmanesh, M. Torkaman, and F. Beiraghdar, "A Case of Classic Galactosemia Manifesting as Neonatal Early and Profound Indirect Hyperbilirubinemia," *Turkish Archives of Pediatrics* 55, no. 3 (2022): 316–319, https://doi.org/10.14744/turkpediatriars.2019.21298.

20. S. Takci, S. Kadayifcilar, T. Coskun, S. Yigit, and B. Hismi, "A Rare Galactosemia Complication: Vitreous Hemorrhage," *JIMD Reports – Case and Research Reports* 5 (2012): 89–93, https://doi.org/10.1007/8904_2011_103.

21. L. Welling, L. E. Bernstein, G. T. Berry, et al., "International Clinical Guideline for the Management of Classical Galactosemia: Diagnosis, Treatment, and Follow-Up," *Journal of Inherited Metabolic Disease* 40, no. 2 (2017): 171–176, https://doi.org/10.1007/s10545-016-9990-5.

22. M. E. Rubio-Gozalbo, M. Haskovic, A. M. Bosch, et al., "The Natural History of Classic Galactosemia: Lessons From the GalNet Registry," *Orphanet Journal of Rare Diseases* 14, no. 1 (2019): 86, https://doi.org/10.1186/s13023-019-1047-z.

23. R. J. Pollitt, A. Green, M. C. CJ, et al., "Neonatal Screening for Inborn Errors of Metabolism: Cost, Yield and Outcome: A Review," *Health Technology Assessment* 1, no. 7 (1997): i–iv, https://doi.org/10.3310/hta1070.

24. S. Schweitzer-Krantz, "Early Diagnosis of Inherited Metabolic Disorders Towards Improving Outcome: The Controversial Issue of Galactosaemia," *European Journal of Pediatrics* 162, no. 1 (2003): S50–S53, https://doi.org/10.1007/s00431-003-1352-2.

25. V. Shah, S. Friedman, A. Moore, B. Platt, and A. Feigenbaum, "Selective Screening for Neonatal Galactosemia: An Alternative Approach," *Acta Paediatrica* 90, no. 8 (2001): 948–949, https://doi.org/10.1111/j.1651-2227.2001.tb02463.x.

26. S. E. Waisbren, C. Y. Read, M. Ampola, et al., "Newborn Screening Compared to Clinical Identification of Biochemical Genetic Disorders," *Journal of Inherited Metabolic Disease* 25, no. 7 (2002): 599–600, https://doi.org/10.1023/A:1022003726224.

27. J. H. Walter, "Arguments for Early Screening: A Clinician's Perspective," *European Journal of Pediatrics* 162, no. 1 (2003): S2–S4, https://doi.org/10.1007/s00431-003-1340-6.

28. I. Badiu Tișa, A. C. Achim, and A. Cozma-Petruț, "The Importance of Neonatal Screening for Galactosemia," *Nutrients* 15, no. 1 (2023): 10, https://doi.org/10.3390/nu15010010.

29. N. Hatam, M. Askarian, S. Shirvani, and E. Siavashi, "Neonatal Screening: Cost-Utility Analysis for Galactosemia," *Iranian Journal of Public Health* 46, no. 1 (2017): 112–119.

30. M. A. Kotb, L. Mansour, and R. A. Shamma, "Screening for Galactosemia: Is There a Place for It?," *International Journal of General Medicine* 12 (2019): 193–205, https://doi.org/10.2147/IJGM.S180706.

31. M. Moody, M. Hosseini, A. Deezagi, P. Yaghmaei, and S. M. Houshmand, The Genetic Basis of Galactosemia in Iranian Patients:

Identification of Twenty Novel Mutations in GALT, GALK1 and GALE Gene Published online June 26, 2023, https://doi.org/10.21203/rs.3.rs-3093450/v1.

32. Y. c. Wang, L. c. Lan, X. Yang, J. Xiao, H. x. Liu, and Q. w. Shan, "A Case Report of Classic Galactosemia With a GALT Gene Variant and a Literature Review," *BMC Pediatrics* 24, no. 1 (2024): 352, https://doi.org/10.1186/s12887-024-04769-0.

33. S. Senemar, A. H. Ganjekarimi, S. Senemar, B. Tarami, and M. Bazrgar, "The Prevalence and Clinical Study of Galactosemia Disease in a Pilot Screening Program of Neonates, Southern Iran," *Iranian Journal of Public Health* 40, no. 4 (2011): 99–104.

34. M. Alieh, P. Narjes, K. Zohreh, et al., "The Incidence and Clinical Study of Galactosemia in Fars Province in South of Iran (Short Communication)," *Galen Medical Journal* 3, no. 1 (2014): 39–45, https://sid.ir/paper/332565/en.

35. M. Shakiba, M. Yasaei, H. Saneifard, et al., "Expanded Inherited Metabolic Diseases Screening by Tandem Mass Spectrophotometry: The First Report From Iran," *Molecular Genetics and Metabolism Reports* 40 (2024): 101103, https://doi.org/10.1016/j.ymgmr.2024.101103.

36. M. M. Welsink-Karssies, S. Ferdinandusse, G. J. Geurtsen, et al., "Deep Phenotyping Classical Galactosemia: Clinical Outcomes and Biochemical Markers," *Brain Communications* 2, no. 1 (2020): fcaa006, https://doi.org/10.1093/braincomms/fcaa006.

37. B. Delnoy, A. I. Coelho, and M. E. Rubio-Gozalbo, "Current and Future Treatments for Classic Galactosemia," *Journal of Personalized Medicine* 11, no. 2 (2021): 75, https://doi.org/10.3390/jpm11020075.

38. L. A. Batey, C. K. Welt, F. Rohr, et al., "Skeletal Health in Adult Patients With Classic Galactosemia," *Osteoporosis International* 24, no. 2 (2013): 501–509, https://doi.org/10.1007/s00198-012-1983-0.

39. A. B. Frederick, A. M. Zinsli, G. Carlock, K. Conneely, and J. L. Fridovich-Keil, "Presentation, Progression, and Predictors of Ovarian Insufficiency in Classic Galactosemia," *Journal of Inherited Metabolic Disease* 41, no. 5 (2018): 785–790, https://doi.org/10.1007/s10545-018-0177-0.