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CASE REPORT

The Role of Proton Magnetic Resonance Spectroscopy in the Diagnosis of Galactosemia in Neonates

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ABSTRACT

Classic galactosemia, the most common form of galactosemia, is a disorder of galactose metabolism caused by the hereditary deficiency of the galactose-1-phosphate uridyl transferase (GALT) enzyme. Life-threatening toxic symptoms and brain edema occur during the neonatal period due to the accumulation of galactose and its metabolites in the tissues of patients without galactose restriction. Galactitol, a toxic substance that accumulates in the brain, is identified as abnormal peaks in Magnetic Resonance Spectroscopy (MRS). We have reported a 22-day-old galactosemic neonate diagnosed with a galactitol peak in brain MRS. Brain H-MRS is a valuable method for early diagnosis of galactosemia patients.

Keywords: Galactosemia. Proton magnetic resonance spectroscopy. Newborn.

Yenidoğanlarda Galaktozemi Tanısında Proton Manyetik Rezonans Spektroskopisinin Yeri

ÖZET

Klasik galaktozemi, galaktozeminin en sık görülen formu olup, galaktoz-1-fosfat uridil transferaz enziminin kalıtsal eksikliğinden kaynaklanan bir galaktoz metabolizması bozukluğudur. Galaktoz kısıtlaması olmayan hastaların dokularında galaktoz ve metabolitlerinin birikmesi nedeniyle yenidoğan döneminde yaşamı tehdit eden toksik semptomlar ve beyin ödemi ortaya çıkar. Beyinde biriken bu toksik maddelerden galaktitol, Manyetik Rezonans Spektroskopisi'nde (MRS) anormal pikler olarak tespit edilir. Beyin MRS'de galaktitol piki ile galaktozemi tanısı konulan 22 günlük bir yenidoğan olgusunu raporladık. Beyin MRS, galaktozemi hastalarının erken tanısı için değerli bir yöntemdir.

Anahtar Kelimeler: Galaktozemi. Proton manyetik rezonans spektroskopisi. Yenidoğan.

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Galactosemia occurs due to the deficiency of one of the three enzymes involved in galactose metabolism: galactokinase, GALT, and uridine diphosphate galactose-4-epimerase. The most common and severe form is classical galactosemia, resulting from an autosomal recessive deficiency of the GALT enzyme[1]. The frequency of classical galactosemia is reported to be between 1/23000-44000[1]. Although the incidence in our country has been reported as 1 in 23775 live births, it is estimated to be more common in regions with a high rate of consanguineous marriage[2]. A life-threatening clinical picture occurs during the neonatal period when a galactosemic infant is fed lactose-containing formula or breast milk. The accumulation

of galactitol in the tissues leads to brain edema and cataracts[1].

Methods used to diagnose classical galactosemia include measuring galactose and galactitol levels in urine, determining the increase in galactose-1-phosphate concentration in erythrocytes, and measuring GALT enzyme activity in erythrocytes[1]. Additionally, brain MRS, which shows the accumulation of abnormal galactitol, has recently been used as a valuable method for diagnosing galactosemia[3,4]. This article presents a galactosemic newborn infant diagnosed through MRS.

Case Report

A twenty-two-day-old female patient was admitted to the emergency department with complaints of drowsiness, poor nutrition, abdominal distention, and jaundice. She was born mature via cesarean section, with an Apgar score of 8-10. The patient's parents were third-degree relatives, and she had a sibling who died in the neonatal period. Physical examination revealed a weight of 3100 gr (10-50 p), a height of 50.5 cm (10-50 p), and a head circumference of 36 cm (10 p). Her general condition was poor, with decreased newborn reflexes and acid and hepatosplenomegaly present in the abdomen. The anterior fontanelle was tense and bulging. The onset of cataracts was seen on the eye examination. Metabolic acidosis, deterioration in liver function tests, direct hyperbilirubinemia, anemia, and thrombocytopenia were observed, while blood glucose and ammonia levels remained normal. Her brain MR imaging and MRS studies were performed after her metabolic tests were taken. MR examinations were performed using a 3-T MRI device "Achieva; Philips Healthcare, Best, The Netherlands" with a 32-channel head coil.

A single voxel (voxel size: 17X17X17 mm) proton MR spectroscopy (PRESS) was performed from the left centrum semiovale at short and intermediate echo times (TE, 35 and 144 ms). At MRS results, the spectrum taken at the short TE value displayed abnormal, very prominent doublet peaks in the region of 3.6-3.8 ppm (Figure 1). These signals, concerning the baseline, were reversed in the second spectrum with medium TE value (Figure 1). This appearance is characteristic of carbohydrate signals and is indicative of galactitol accumulation.

A lactose-free diet was given to the patient with the diagnosis of galactosemia. The patient's metabolic tests were also found to be consistent with galactosemia. The positive reductant (+++) in urine, high galactose excretion in urine sugar chromatography, and high galactose 1-Phosphate level were detected.

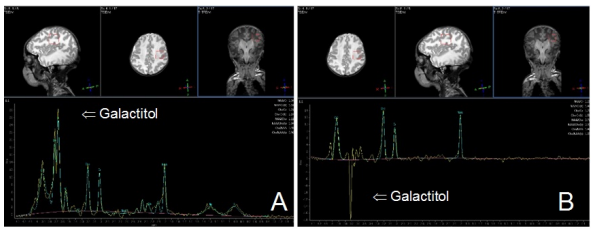

Figure 1.
Single-voxel MR spectroscopy images obtained from the left centrum semiovale in short TE (A) and intermediate TE (B) values. Abnormal doublet peaks (galactitol) arising in the region of 3.6- 3.8 ppm in the spectrum obtained by short TE. In the spectrum obtained with the intermediate TE galactitol peak is reversed (indicated by arrow).

Clinical findings, liver functions, hematological examinations, and acidosis were resolved during the patient's follow-up. A homozygous F294Y mutation was identified in the genetic test, confirming the diagnosis of galactosemia (HGMD No: CM 990667). In the follow-up MRS of the patient 4 months later, the galactitol peak was significantly regressed (Figure 2).

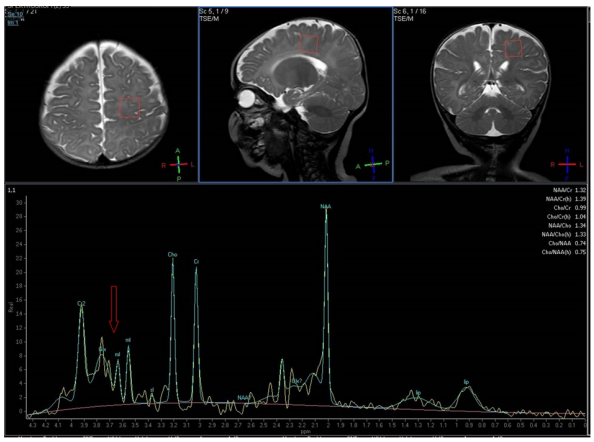

Figure 2.
In the single voxel MR spectroscopy images after treatment, the amplitude of the abnormal galactitol doublet, which appeared in the range of 3.6- 3.8 ppm in the spectrum obtained with short TE time, decreased markedly (indicated by arrow).

Discussion and Conclusion

There may be untreated galactosemic infants with galactose toxicity and brain edema who require neonatal intensive care. This severe clinical presentation is not specific to any one disease but is a confusing condition requiring many differential diagnoses. Specific tests used to diagnose classical galactosemia include the measurement of galactose and galactitol in urine, determination of elevated galactose 1-phosphate concentration in erythrocytes,

and the measurement of GALT enzyme activity in erythrocytes which is the gold standard method for diagnosis[1]. In addition, MRS, which enables the display of galactitol peak in the brain, can also be used as a rapid diagnostic method.

Galactose-1P and galactitol are thought to be the metabolites responsible for pathogenesis affecting the liver, kidney, lens, and brain[5]. Accumulation of galactitol in the brain because of galactosemia has also been demonstrated by autopsy[6].

A few cases have been reported in the literature that have been diagnosed with galactosemia by demonstrating specific galactitol accumulation through MRS[3,4,7-10]. In the brain MRS of galactosemic newborns reported by these investigations, galactitol peak was found in the brain between 3.67-3.74 ppm[3,4,7-10]. It was also observed that the abnormal carbohydrate peak disappeared in MRS after treatment[8].

In our patient's MRS examination, very prominent doublet peaks were also found in the region of 3.6-3.8 ppm, abnormally in the spectrum obtained at short TE, consistent with the literature data. In the spectrum obtained at the intermediate TE value, this doublet peak was observed to be reversed relative to the baseline. No significant abnormality was found in the proportion of basal brain metabolites. In the literature, the presence of unusual peaks in the 3.7 ppm region due to the accumulation of carbohydrates in the MR spectroscopy of patients with carbohydrate metabolism disorder (glucose in diabetes mellitus, galactitol in galactosemia, arabitol and ribitol in polyol metabolism disorder) was reported[8]. In vitro MRS studies have been used to distinguish them[7]. Based on these studies, the detected peak in MRS was considered to be due to the accumulation of galactitol when evaluated together with the patient's clinic. These studies did not include the intermediate TE value data. The patient's symptoms improved with diet, and the diagnosis of galactosemia was confirmed through genetic testing.

Galactitol peaks were not detected in the MRS examinations performed during adulthood in patients who had received treatment for galactosemia. Therefore, MRS is only beneficial for patients with untreated galactosemia[7,10].

Brain MRS is a valuable method for early diagnosis of patients with galactosemia. The brain MRS method applied to newborn infants exhibiting acute central nervous system manifestations may complement cranial imaging, especially in diagnosing metabolic diseases. The peaks detected in the brain MRS of these patients, which are not normally seen, should be examined in detail. Brain MRS can be used as a useful method for assessing the treatment response of galactosemia patients in the newborn period and follow-up.

Ethics Committee Approval Information:
No personal data was shared in our case presentation and no Ethics committee approval was sought.

Researcher Contribution Statement:
Idea and design: S.C.C., C.G.O., B.A.D., H.Ö., N.K., S.Y., Ş.E.; Data collection and processing: S.C.C., C.G.O., B.A.D., H.Ö., N.K., S.Y., Ş.E.; Analysis and interpretation of data: S.C.C., C.G.O., B.A.D., H.Ö., N.K., S.Y., Ş.E.; Writing of significant parts of the article: S.C.C., C.G.O., B.A.D., S.Y.

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References

1. Bosch AM. Classical galactosaemia revisited. J Inherit Metab Dis. 2006; 29 (4): 516–525.
2. Çelik M, Akdeniz O, Ozbek MN, Kirbiyik O. Neonatal classic galactosemia—diagnosis, clinical profile and molecular characteristics in unscreened Turkish population. J Trop Pediatr. 2022; 68(6): 1–8.
3. Rossi-Espagnet MC, Sudhakar S, Fontana E, et al. Neuroradiologic Phenotyping of Galactosemia: From the Neonatal Form to the Chronic Stage. AJNR Am J Neuroradiol. 2021; 42 (3): 590-596.
4. Cakmakci H, Pekcevik Y, Yis U, Unalp A, Kurul S. Diagnostic value of proton MR spectroscopy and diffusion-weighted MR imaging in childhood inherited neurometabolic brain diseases and review of the literature. Eur J Radiol. 2010; 74 (3): 161–171.
5. Berry GT, Walter JH, Fridovich-Keil JL. Disorders of galactose metabolism. Saudubray JM, Baumgartner MR, Garcia-Cazorla A, Walter J, editors. Inborn Metabolic Diseases: Diagnosis And Treatment. (7th ed). e-Book: Springer; 2022.p.315-325.
6. Quan-Ma R, Wells HJ, Wells WW, Sherman FE, Egan TJ. Galactitol in the tissues of a galactosemic child. Am J Dis Child. 1966; 112 (5): 477-478.
7. Berry GT, Hunter JV, Wang Z, et al. In vivo evidence of brain galactitol accumulation in an infant with galactosemia and encephalopathy. J Pediatr. 2001; 138 (2): 260–262.
8. Otaduy MCG, Leite CC, Lacerda MTC, et al. Proton MR spectroscopy and imaging of a galactosemic patient before and after dietary treatment. AJNR Am J Neuroradiol. 2006; 27 (1): 204–207.
9. Martinelli D, Bernardi B, Napolitano A, Colafati GS, Dionisi-Vici C. Teaching NeuroImages: Galactitol peak and fatal cerebral edema in classic galactosemia: too much sugar in the brain. Neurology. 2016; 86 (3): e32–e33.
10. Wang ZJ, Berry GT, Dreha SF, Zhao H, Segal S, Zimmerman RA. Proton magnetic resonance spectroscopy of brain metabolites in galactosemia. Ann Neurol. 2001; 50 (2): 266–269.