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A case of Krabbe disease presenting with hydrocephalus

Hidrosefali ile başvuran bir Krabbe hastalığı olgusu

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ABSTRACT

Krabbe disease, or globoid cell leukodystrophy, is a rare autosomal recessive lysosomal storage disorder caused by deficiency of galactocerebrosidase (GALC) enzyme activity. While classic infantile presentation typically includes irritability, spasticity, and developmental regression, this report describes an atypical initial manifestation with acute hydrocephalus. A four-month-old female infant, born to consanguineous parents, presented with poor feeding, lethargy, hypotonia, and episodic staring. Physical examination revealed failure to thrive with normal head circumference. Neuroimaging demonstrated acute hydrocephalus and characteristic white matter abnormalities including T2 hyperintensities in the dentate nucleus and internal capsule. Cerebrospinal fluid (CSF) analysis showed significantly elevated protein levels. The diagnosis was confirmed through markedly reduced galactocerebrosidase activity (0.2 nmol/hour/mg protein; reference >0.3) and identification of a homozygous pathogenic variant in the GALC gene (c.908C>T p.Ser303Phe). This case emphasizes that acute hydrocephalus can represent an uncommon but critical presenting feature of infantile Krabbe disease. In infants with unexplained neurological deterioration and hydrocephalus, particularly with consanguineous family history, prompt metabolic evaluation including cerebrospinal fluid analysis and specific enzyme assays is essential for diagnosis. Early identification remains crucial for considering potential therapeutic interventions, including hematopoietic stem cell transplantation.

Keywords: Krabbe disease, hydrocephalus, galactocerebrosidase, lysosomal storage disease, *GALC* gene

ÖZ

Krabbe hastalığı veya globoid hücreli lökodistrofi, galaktoserebrosidaz (GALC) enzim aktivitesi eksikliğinin neden olduğu nadir, otozomal resesif geçişli bir lizozomal depo hastalığıdır. Klasik infantil başlangıç tipik olarak irritabilite, spastisite ve gelişim geriliği içerirken, bu olgu sunumu akut hidrosefali ile giden atipik bir ilk bulguyu tanımlamaktadır. Akraba anne babadan doğan dört aylık kız bebek beslenme güçlüğü, letarji, hipotoni ve epizodik sabit bakış şikâyetleriyle başvurdu. Fizik muayenede baş çevresi normaldi ve gelişme geriliği saptandı. Nörogörüntülemede akut hidrosefali ve dentat nükleus ile internal kapsülde T2 hiperintensitelerini içeren karakteristik beyaz cevher anormallikleri izlendi. Beyin omurilik sıvısı (BOS) analizinde protein seviyelerinin belirgin şekilde arttığı görüldü. Tanı, belirgin derecede azalmış galaktoserebrosidaz aktivitesi (0,2 nmol/saat/mg protein; referans >0,3) ve GALC geninde homozigot patojenik bir varyantın (c.908C>T p.Ser303Phe) saptanmasıyla doğrulandı. Bu olgu, akut hidrosefalinin infantil Krabbe hastalığının nadir fakat kritik bir başlangıç bulgusu olabileceğini vurgulamaktadır. Açıklanamayan nörolojik gerileme ve hidrosefalisi olan bebeklerde, özellikle akraba evliliği öyküsü varlığında, BOS analizi ve spesifik enzim testlerini içeren hızlı metabolik değerlendirme tanı için esastır. Erken tanı, hematopoietik kök hücre nakli de dâhil olmak üzere potansiyel terapötik müdahalelerin değerlendirilmesi için kritik önem taşımaktadır.

Anahtar Sözcükler: *Krabbe hastalığı, hidrosefali, galaktoserebrosidaz, lizozomal depo hastalığı, GALC geni*

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INTRODUCTION

Krabbe disease (globoid cell leukodystrophy) is a devastating neurodegenerative disorder resulting from deficient galactocerebrosidase (GALC) activity, leading to the accumulation of cytotoxic lipids such as psychosine (galactosylsphingosine) (1). This accumulation causes progressive demyelination in the central and peripheral nervous systems. The disease exhibits a spectrum of severity, classically divided into early infantile, late infantile, juvenile, and adult-onset forms. Common clinical features in the infantile form include extreme irritability, feeding difficulties, developmental regression, spasticity, seizures, and eventual decerebration. This report details an atypical case where acute hydrocephalus was the initial dominant clinical feature, underscoring the phenotypic variability of this disorder (2).

CASE REPORT

A four-month-old female infant, the product of a first-degree consanguineous marriage, was admitted to our department with complaints of poor sucking, lethargy, generalized hypotonia, and episodic staring spells suggestive of seizures. She was born at term via normal spontaneous vaginal delivery with a birth weight of 2000 grams. Her postnatal history was unremarkable.

Physical examination revealed significant failure to thrive, but her head circumference was within normal percentiles for her age. Neurological assessment confirmed marked hypotonia. Brain magnetic resonance imaging (MRI) was striking for acute hydrocephalus. Additionally, it showed characteristic T2 hyperintensities in the periventricular white matter, dentate nucleus, and internal capsule, alongside mild thickening of the optic chiasm and prechiasmatic optic nerve as seen in (Figure 1-2). Echocardiography and abdominal ultrasonography were normal. Fundoscopic examination identified papilledema and mild temporal disc pallor.

Initial metabolic screening, including plasma amino acids, urine organic acids, tandem mass spectrometry, very long-chain fatty acids, and transferrin isoelectric focusing were normal. However, cerebrospinal fluid analysis demonstrated a markedly elevated protein concentration (2400 mg/dL, RR: 15-45 mg/dL). This finding prompted specific lysosomal enzyme testing, which revealed a profoundly reduced GALC activity of 0.2 nmol/hour/mg protein (reference range >0.3). Subsequent genetic analysis of the *GALC* gene revealed a homozygous pathogenic variant, c.908C>T (p.Ser303Phe), that confirms the diagnosis of Krabbe disease. The variant is listed in the dbSNP database with rs756352952 number and is reported pathogenic in the ClinVar database with Variation ID: 280957 and Accession Number: VCV000280957.68. The variant met the following ACMG/AMP 2015 criteria: PS3, PM2, PM3, PP2, PP3, and PP5. The patient was enrolled in a palliative and supportive care follow-up program.

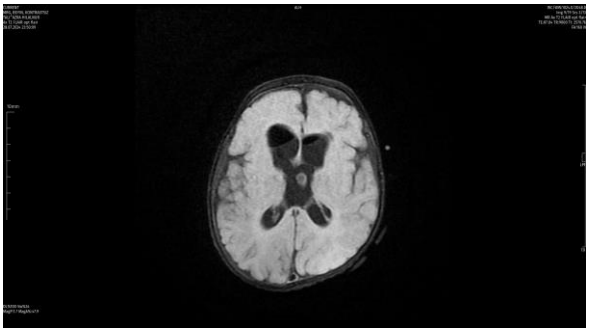

Figure-1. Axial FLAIR MRI shows characteristic hyperintense lesions predominantly in the periventricular white matter.

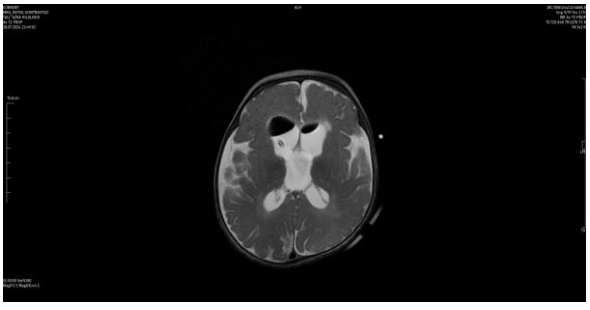

Figure-2. Axial T2-weighted MRI sequence revealing marked ventricular dilatation, consistent with acute hydrocephalus

DISCUSSION

This report highlights acute hydrocephalus, a rare yet severe neurological complication, as the initial manifestation of infantile Krabbe disease. While hydrocephalus is not among the most frequently reported initial symptoms, its occurrence can be explained by the underlying pathophysiology. The accumulation of psychosine is profoundly toxic to oligodendrocytes and Schwann cells, leading to widespread demyelination, astrogliosis, and the formation of characteristic multinucleated globoid

cells. This neuroinflammatory process can disrupt normal cerebrospinal fluid dynamics, potentially by obstructing CSF pathways or impairing reabsorption at the arachnoid granulations, thereby precipitating hydrocephalus (1). The significant elevation of CSF protein in our patient further supports intense central nervous system inflammation and blood-brain barrier disruption (2, 3).

The *GALC* genetic mutation identified in our patient, c.908C>T (p.Ser303Phe) rs756352952 is classified as a pathogenic variant with a severe outcome. Our patient's presentation at four months of age aligns with the natural history of the infantile form, where the median age of onset is reported to be around 4 months, with a median survival of 1.5 years if untreated (2).

The diagnostic journey in this case highlights several key points. First, normal results from standard metabolic screens do not rule out lysosomal storage disorders like Krabbe disease. Second, the combination of specific neuroimaging like white matter changes and high CSF protein levels should consider leukodystrophy. The definitive diagnosis rests on demonstrating deficient *GALC* enzyme activity and corroborating it with molecular genetic analysis (5).

This patient presented at a stage where the opportunity for effective intervention with hematopoietic stem cell transplantation (HSCT) was probably lost. The efficacy of HSCT, the sole disease-modifying therapy for Krabbe disease, is critically dependent on its application before or in the earliest stages of symptom manifestation (5, 6). Studies have shown that for optimal outcomes in infantile cases, HSCT should ideally be performed within the first 4-6 weeks of life (6). This underscores the importance of newborn screening (NBS) programs that utilize GALC enzyme assay in dried blood spots, often supplemented with second tier tests like psychosine measurement, to identify at risk infants before symptom onset (5, 6). The experience from New York State's NBS program, while identifying challenges, has solidified the need for a rapid, coordinated system from screening to treatment referral (6).

Looking forward, therapeutic horizons are expanding. Preclinical studies in the twitcher mouse model, the authentic murine model of Krabbe disease, have shown remarkable success with intravenously administered adeno-associated virus (AAV) gene therapy, both alone and in combination with HSCT (4, 7). These approaches have demonstrated normalization of GALC activity, preservation of myelination, and dramatic extensions in lifespan, offering hope for more effective future treatments that could address the pervasive neurological damage, including complications (7).

CONCLUSION

This report highlights hydrocephalus as a potential and serious symptom of infantile Krabbe disease. This report emphasizes that clinicians should consider lysosomal storage diseases in the differential diagnosis of infants presenting with unexplained neurological deterioration and hydrocephalus, particularly when there is a history of consanguinity. A diagnostic approach involving neuroimaging, CSF protein analysis, and specific enzymatic and genetic testing is crucial. In Krabbe disease, a clear genotype-phenotype correlation dictates the clinical onset and severity of the condition, primarily determined by the specific combination of *GALC* variants. Infantile-onset Krabbe disease is driven by a profound loss of galactocerebrosidase activity, typically resulting from homozygosity for the common 30-kb *GALC* deletion or compound heterozygosity involving this deletion paired with other severe pathogenic variants, such as nonsense or frameshift mutations. Conversely, later-onset Krabbe disease is closely linked to specific genetic profiles that likely preserve some residual enzyme function. This delayed phenotype is consistently observed in individuals carrying specific missense variants—such as p.Gly286Asp, p.Thr112Ala, or p.Leu634Ser—either in a homozygous state or compounded with the 30-kb deletion or other severe alleles. Ultimately, the nature and pairing of these specific alleles directly predict whether a patient will present with the severe infantile form or a later-onset phenotype (8). Parental screening plays a critical role in the prevention of the disease. Furthermore, cases involving intrauterine affection and subsequent termination of pregnancy have been reported in the literature (9). Although treatment options are limited if diagnosis is delayed, the ongoing development of advanced therapies such as gene therapy offers significant promise. Ultimately, the best outcomes will continue to depend on early diagnosis, for which newborn screening and high clinical awareness will remain cornerstones.

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