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ORIGINAL RESEARCH
Pediatric Emergency

Evaluation of serum galectin-3 levels of patients with familial Mediterranean fever (FMF) admitted to the pediatric emergency service

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ABSTRACT

Objective: Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disorder predominantly affecting individuals of Mediterranean descent, including those from countries such as Türkiye, Armenia, Arab nations, and Sephardic Jews. It is characterized by recurrent episodes of fever and inflammation affecting the abdomen, chest, and joints. Galectin-3, a β-galactoside-binding lectin, plays a significant role in inflammation. However, its role in FMF and its relationship with disease activity and severity remains unclear, warranting further investigation. This study aims to compare serum galectin-3 levels between FMF patients and healthy children, evaluating its diagnostic potential and its correlation with disease activity in FMF. Ultimately, this research seeks to better understand the role of galectin-3 in FMF and assess its potential as a biomarker.

Material and Methods: Between September 1, 2022, and February 1, 2023, 32 FMF patients who presented to our pediatric emergency department were included in this study. The control group consisted of 30 age- and gender-matched healthy children. Simultaneously, hemogram and CRP tests were conducted.

Results: No statistically significant differences were found between the control group and FMF patients in terms of galectin-3 levels and platelet counts ($p>0.05$). Furthermore, no significant correlation was observed between galectin-3 levels and CRP values in the patient groups.

Conclusion: There was no significant difference in serum galectin-3 levels between FMF patients and healthy controls.

Keywords: Control; familial Mediterranean fever; galectin-3; pediatric patients; serum.

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Çocuk acil servisine başvuran ailevi Akdeniz ateşi (AAA) hastalarının serum galektin-3 düzeylerinin değerlendirilmesi

ÖZET

Amaç: Ailevi Akdeniz Ateşi (FMF), özellikle Türkiye, Ermenistan, Arap ülkeleri ve Sefarad Yahudileri gibi Akdeniz kökenli toplulukları etkileyen kalıtsal bir otoinflamatuar hastalıktır. Karın, göğüs ve eklemleri etkileyen tekrarlayan ateş ve inflamasyon atakları ile karakterizedir. β-galaktozid bağlayıcı bir lektin olan galektin-3, inflamasyon süreçlerinde önemli bir rol oynamaktadır. Ancak FMF hastalığındaki rolü ve hastalık aktivitesi ile ilişkisi hâlâ net değildir. Bu çalışmanın amacı, FMF hastaları ile sağlıklı çocuklar arasında serum galektin-3 düzeylerini karşılaştırmak; galektin-3'ün tanısal potansiyelini ve hastalık aktivitesi ile olan ilişkisini değerlendirmektir.

Gereç ve Yöntemler: 1 Eylül 2022 – 1 Şubat 2023 tarihleri arasında çocuk acil servisine başvuran 32 FMF hastası ile yaş ve cinsiyet açısından eşleştirilmiş 30 sağlıklı çocuk çalışmaya dahil edilmiştir. Tüm katılımcılardan eş zamanlı olarak hemogram ve CRP örnekleri alınmıştır. Serum galektin-3 düzeyleri kemilüminesan mikropartikül immünassay (CMIA) yöntemiyle analiz edilmiştir.

Bulgular: FMF hastaları ile kontrol grubu arasında galektin-3 düzeyleri ve trombosit sayıları açısından istatistiksel olarak anlamlı bir fark saptanmamıştır ($p>0.05$). Galektin-3 ile CRP düzeyleri arasında da anlamlı bir korelasyon bulunmamıştır. ROC analizi sonucunda galektin-3'ün FMF tanısında etkili bir biyobelirteç olmadığı belirlenmiştir ($p>0.05$).

Tartışma: FMF hastaları ile sağlıklı bireyler arasında serum galektin-3 düzeyleri açısından anlamlı bir fark bulunmamıştır. Galektin-3'ün FMF hastalığında tanısal bir belirteç olarak kullanımı sınırlı görünmektedir. Daha geniş örneklem gruplarıyla yapılacak ileri çalışmalar galektin-3'ün hastalık sürecindeki rolünü daha iyi ortaya koyabilir.

Anahtar Kelimeler: Ailevi Akdeniz ateşi; çocuk hastalar; galektin-3; kontrol; serum.

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INTRODUCTION

Autoinflammatory diseases are characterized by seemingly unprovoked inflammation (1).

The first described and most common autoinflammatory disease is familial Mediterranean fever (FMF). Mutations in the MEFV gene disrupt the regulation of pyrin, leading to the activation of caspase-1. Pyrin protein is expressed mainly in granulocytes and dendritic cells, as well as in serosal and synovial fibroblasts. The characteristic clinical manifestations of FMF are febrile and poly-serositis attacks that resolve spontaneously in 1–3 days (2).

Galectin-3 (gal-3) is a β-galactoside-binding lectin involved in regulating cell-cell and extracellular interactions. It plays a role in recognizing self and non-self antigens, as well as in cellular activation, proliferation, differentiation, migration, and apoptosis (3–5). Galectin-3 plays a significant role in cellular and tissue pathophysiology by organizing niches that drive inflammation and immune responses and is expressed in many types of cells, including neutrophils, dendritic cells, monocytes, macrophages, and all types of immune cells. Elevated serum galectin-3 levels have been observed in numerous pathological conditions (6, 7).

Previous studies, such as those by Yilmaz et al. (8), have shown that serum galectin-3 levels are higher in FMF patients compared to healthy controls. Sundqvist et al. (9) assessed galectin-3 levels in five PFAPA patients during attacks and control subjects.

Our study aimed to evaluate the serum galectin-3 concentration and explore its potential association with disease activity and severity indexes in patients with FMF manifestations.

MATERIAL AND METHODS

This cross-sectional study included 32 children with FMF, who were evaluated in our pediatric emergency department between September 2022 and February 2023. All patients met at least one of the Pediatric FMF criteria or the Eurofever/Pediatric Rheumatology International Trials Organization (PRINTO) 2019 classification criteria for FMF. The control group consisted of 30 healthy children matched for age and gender.

Simultaneous hemogram tests (neutrophil, lymphocyte, neutrophil/lymphocyte ratio, platelets, MPV) and CRP levels were measured. Serum galectin-3 levels were assessed using chemiluminescent microparticle immunoassay (CMIA) with Abbott reagents on the Architect ci8200 analyzer. Biochemical assays, such as CRP, were measured using the immunoturbidimetric method on the same analyzer. This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Health Sciences University

Table 1. Comparison between groups in terms of galectin-3, CRP, platelet and hemoglobin values of FMF patients and healthy group

	Group	n	Mean±SD	Median (IQR)	Test value	p
Galectin-3 (ng/mL)	Patient	32	0.31±0.24	0.27 (0.31)	-1.036	0.300**
	Control	30	0.38±0.26	0.32 (0.31)		
CRP	Patient	32	49.19±66.93	10.75 (78.78)	-4.546	0.000**
	Control	30	2.7±6.03	0.35 (1.88)		
Platelets	Patient	32	291558.4±78234	284500 (104000)	-0.984	0.329*
	Control	30	350300±114667.5	342000 (125000)		
Hemoglobin	Patient	32	11.8±1.5	11.7 (1.65)	3.912	0.000*
	Control	30	12.02±1.4	12.05 (1.6)		

SD: Standard deviation; IQR: Interquartile range; CRP: C reactive protein; *: Independent t test; **: Man-Whitney U test.

Ümraniye Training and Research Hospital (Approval number: E-54132726-000-18346/261). Informed consent was obtained from all participants or their guardians. We offered comprehensive information about the study, including its objectives, potential risks, and benefits of participation, to ensure informed consent from participants. We also ensured that participants were free to withdraw from the study at any time without any adverse consequences. We ensured the confidentiality and privacy of all participants by using codes instead of names and by storing all data in a secure database that was only accessible to the research team.

Blood samples were obtained from patients with FMF disease and healthy individuals via peripheral vein puncture. The sera were then separated by centrifugation at 1500 x g for 10 minutes at room temperature and stored at -86 °C until analysis.

Galectin-3 concentration was assessed using the chemiluminescent microparticle immunoassay with Abbott reagents on the Architect ci8200 analyzer. Biochemical assays were conducted using the immunoturbidimetric method on the same analyzer. Hemoglobin levels and platelets were determined using standard procedures on the Sysmex XS-800i analyzer.

Statistical Analysis

The Kolmogorov–Smirnov test was used to assess the normality of data distribution. Descriptive statistics, including mean, standard deviation, median, interquartile range (IQR), and frequency, were used to summarize the study variables. For comparisons between FMF patients and healthy controls, the Student's t-test was applied to normally distributed variables, and the Mann–Whitney U test was used for non-normally distributed variables.

Correlation analysis was conducted to evaluate relationships between galectin-3 levels and other inflammatory markers such as CRP. To assess the diagnostic performance of galectin-3, a Receiver Operating Characteristic (ROC) analysis was performed.

A p-value of less than 0.05 was considered statistically significant. All analyses were carried out using (insert software, e.g., SPSS version 25.0).

RESULTS

An overview of the demographic and laboratory data for all participants, including individuals diagnosed with FMF disease and healthy subjects, can be found in Table 1.

Comparison between FMF patients and the control group for galectin-3 and platelet variables showed no statistically significant differences ($p>0.05$). Additionally, the ROC analysis indicated that galectin-3 was not effective in diagnosing FMF ($p>0.05$).

When the control group and FMF patients were compared according to CRP and hemoglobin variables, there was a statistically significant difference ($p<0.05$).

While FMF patients were observed to have higher CRP value averages than the control group, it was determined that the control group had higher hemoglobin value averages.

It was determined that there was no statistically significant relationship between galectin-3 and CRP values of the patient groups (Table 1).

Analysis of musculoskeletal findings, genetic alleles, colchicine use, presence of amyloidosis, proteinuria, and comorbidities revealed no statistically significant differences in relation to galectin-3 values ($p>0.05$).

Descriptive demographic and laboratory data of patients diagnosed with FMF and healthy controls are presented in Table 2. The mean serum galectin-3 level in FMF patients was 0.34±0.25 ng/mL. The average age at onset of attacks was 72.3±49.3 months, while the mean age at diagnosis was 89.20±49.76 months. The average attack duration was 3.0±1.9 days, and the annual number of attacks was 4.8±4.5 (Table 2).

Additionally, the ROC analysis indicated that galectin-3 was not a reliable diagnostic marker for FMF ($p>0.05$) (Fig. 1).

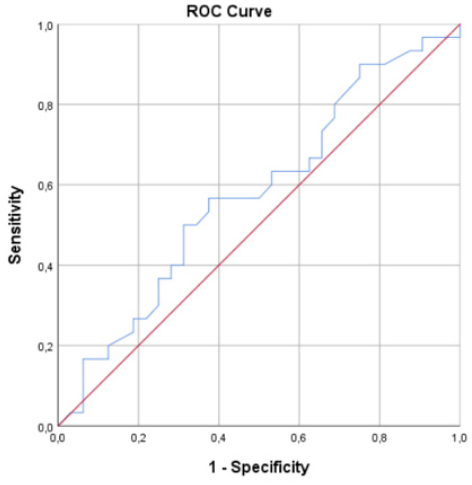
Discussion

The aim of this study was to assess serum galectin-3 levels in FMF patients and investigate its potential role in the disease's pathophysiology.

Table 2. Descriptive statistics

	n	Mean	Standard deviation
Galectin-3 (ng/mL)	32	0.34	0.25
Last examination age (months)	32	111.18	63.55
Diagnosis age (months)	32	89.20	49.76
Age of onset of attacks (months)	32	72.3	49.3
Time between onset of attack and diagnosis (months)	32	36.0	43.4
Attack duration (days)	32	3.0	1.9
Number of attacks per year	32	4.8	4.5
CRP	62	26.69	53.31
WBC	62	10311	4686
Hemoglobin	62	11.91	1.44
Neutrophil	62	6176	3802
Lymphocyte	62	3579.7	1869.0
NLR	62	2.45	2.20
Platelets	62	319981.8	101179.6
MPV	62	8.62	1.27

CRP: C reactive protein; WBC: White blood cells; NLR: Neutrophil-to-lymphocyte ratio; MPV: Mean platelet volume.



AUC	Std Error	p	%95 Confidence Interval	
			Lower Limit	Upper Limit
0.577	0.073	0.301	0.433	0.720

Figure 1. ROC analysis table for galectin-3 value.

FMF is characterized by recurrent fever episodes, elevated inflammatory markers such as C-reactive protein (CRP), and systemic inflammation. However, our study did not find a statistically significant difference in galectin-3 levels between FMF patients and healthy controls. This contrasts with previous studies, such as those by Yılmaz et al. (8), who reported higher galectin-3 concentrations in FMF patients compared to controls (9).

This discrepancy could arise from differences in patient population, disease severity, or other environmental factors not controlled for in the study design. Additionally, FMF is a genetically heterogeneous disease with varying degrees of clinical presentation and inflammatory activity, which may explain the inconsistent findings across studies. It is possible that galectin-3's role in FMF may not be uniform across all patient subgroups.

Galectin-3 (Gal-3) has gained increasing attention due to its prominent role in regulating inflammation and immune responses. It is involved in various biological processes, including cell activation, migration, differentiation, and apoptosis, which are crucial in both physiological and pathological contexts. Elevated galectin-3 levels have been reported in several inflammatory diseases, autoimmune conditions, and cancer, highlighting its potential as a biomarker for disease activity and prognosis (10).

One potential explanation for the lack of correlation between galectin-3 and CRP in our study lies in the nature of both markers. CRP is a well-established acute-phase reactant and a general indicator of systemic inflammation. In contrast, galectin-3's role in FMF may be more closely related to chronic or subclinical inflammation rather than the acute inflammatory phase. Cerri et al. (11) explored the role of galectin-3 in inflammation and tissue repair, particularly in autoimmune diseases, and suggested that galectin-3 plays a crucial role in modulating inflammation and aiding tissue healing. This could explain why galectin-3 levels do not immediately elevate CRP levels during acute inflammation (11).

Despite these findings, our study is limited by the relatively small sample size, which may have affected the statistical power to detect subtle differences between groups. Moreover, the cross-sectional design of the study does not allow for the assessment of the temporal relationship between galectin-3 levels and disease activity over time. Future studies with larger sample sizes and longitudinal follow-up may provide more insights into the potential role of galectin-3 in FMF, particularly in relation to chronic inflammation or as a potential therapeutic target.

CONCLUSION

In conclusion, our study did not demonstrate a significant difference in serum galectin-3 levels between FMF patients and healthy controls, nor did we find any correlation with CRP or disease severity markers. While galectin-3's role in FMF warrants further investigation, our results suggest that it may not serve as a reliable biomarker for diagnosing or assessing disease activity in FMF at this time. Future research should focus on exploring its potential role in the context of chronic inflammation or subclinical disease phases in FMF, as well as its applicability as a therapeutic target.

Ethics Committee Approval: The Health Sciences University Ümraniye Training and Research Hospital Ethics Committee granted approval for this study (date: 08.08.2022, number: E-54132726-000-18346/261).

Informed Consent: Informed consent was obtained from all participants or their guardians.

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Hasta Onamı: Tüm katılımcılardan veya velilerinden bilgilendirilmiş onam alınmıştır.

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