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Original Article

Humoral Immunity Status in Pediatric Patients with Familial Mediterranean Fever: Exploring the Role of IgA

Gökçe Mergan Çetiner[1], Yaşar Kandur[2*], Derya Beyza Sayın Kocakap[3]

1. Department of Pediatrics, School of Medicine, Kırıkkale University, Kırıkkale, Turkey.
2. Department of Pediatric Nephrology, School of Medicine, Kırıkkale University, Kırıkkale, Turkey.
3. Department of Medical Genetics, School of Medicine, Kırıkkale University, Kırıkkale, Turkey.

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Corresponding Author:
Yaşar Kandur, MD.
Address: Department of Pediatric Nephrology, School of Medicine, Kırıkkale University, Kırıkkale, Turkey.
E-mail: yaskan30@yahoo.com

ABSTRACT

Background and Aim: Research on the role of the adaptive immune system in familial Mediterranean fever (FMF) is limited. The aim of this study was to investigate the levels of immunoglobulins (Ig) IgG, IgM, IgA and absolute lymphocyte count (ALC) in FMF patients compared to normal subjects.

Methods: Patients diagnosed with FMF were included in the study. At the time of data entry, we recorded demographic information, mutation type, ALC, eosinophils and levels of IgA, IgG, IgM and IgE. We compared these variables with those of the control group.

Results: Thirty-five FMF patients (M/F=9/26) were included in this study. There was no significant difference between the mean quantitative levels of the immunoglobulins (IgA, IgG and IgM) and Ig E between the patient and control groups (P>0.05). Compared with the biallelic and monoallelic mutations, we found higher Ig A levels in the biallelic group (1.5±0.7 vs 0.9±0.3 mg/dL, respectively P=0.008). An interesting finding was that three patients with homozygous M694 mutation had an Ig A level above the upper limit while.

Conclusion: No significant difference was found in terms of humoral immunity between FMF patients and healthy individuals. However, we believe that IgA levels should be examined in patients with severe FMF manifestations; the finding of high IgA levels in three patients with a homozygous M694V mutation supports our hypothesis.

Keywords: Familial mediterranean fever (FMF), Adaptive immunity, Immunoglobulin A (IgA)

Introduction

Familial Mediterranean fever (FMF) is the most prevalent monogenic autoinflammatory disease, marked by recurrent episodes of fever and polyserositis [1]. FMF is an autoinflammatory rather than an autoimmune disease, where T-regs may play a compensatory and regulatory role concerning proinflammatory cytokines, potentially contributing to the self-resolving nature of the disease. Systemic amyloidosis can result from the persistent inflammation associated with FMF [2]. An FMF mutation activates the inflammasome, which plays a crucial role in innate immunity by activat-

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ing IL-1, thus initiating inflammation [3-5]. Natural killer (NK) cells, cytotoxic lymphocytes that are also part of the innate immune system, are active in FMF and produce cytokines to assist the adaptive immune response [6, 7]. B lymphocytes also contribute to inflammatory pathways in FMF by transforming into immunoglobulin-producing immunoblasts upon activation, which later mature into plasma cells. As far as we know, FMF is predominantly a disorder of the innate immune system; however, there is limited research available on the role of adaptive immune systems in FMF. The aim of this study was to investigate the levels of immunoglobulins IgG, IgM, IgA, and absolute lymphocyte count (ALC) in FMF patients compared to normal control subjects. Additionally, we sought to compare allergic markers (IgE and eosinophils) to reach conclusive results.

Materials and Methods

Patients diagnosed with FMF during the research period were enrolled in the study. The medical records of patients with FMF under the follow-up of our nephrology-rheumatology center between 2018 and 2023 were also retrospectively reviewed. FMF was diagnosed based on the criteria expressed by Livneh et al. [8]. *MEFV* exons underwent PCR amplification by genomic DNA, leading to the detection of the 12 most common *MEFV* mutations (R202Q, E148Q, M694V, P369S, F479L, M680I (G/A), M680I (G/C), M694I, V726A, K695R, A744S, R761H). Twenty age-matched control subjects were included in the study. At the time of data entry, we recorded demographic information, mutation type, ALC, eosinophils, and IgA, IgG, IgM and IgE levels of the patients. The control group consisted of patients who applied to the pediatric outpatient clinic with complaints of frequent illness (especially respiratory tract infections) and had their quantitative immunoglobulin levels measured. We also compared these variables based on mutation type: Biallelic (BA) and monoallelic (MA).

Statistical analysis

Data were analyzed by SPSS software, version 16 at a significance level of $P<0.05$. The student's t-test evaluated differences between the continuous variables in the two groups. Variations in proportions were assessed by the chi-square test.

Results

This study assessed 35 FMF patients (M/F=9/26) with a mean age of 127±53 months referring to the Pediatric Nephrology/Rheumatology Clinic. The control group consisted of 7(35%) females and 13(65%) males with a mean age of 103±57 months. No significant difference was found between the groups in ALC and eosinophil count (P=0.204 and P=0.445, respectively). Also, no significant difference was found between the mean quantitative levels of the immunoglobulins (IgG, IgA and IgM) and IgE between the control and patient groups (P>0.05) (Table 1).

MEFV gene mutation analysis was performed for all patients, and the results are summarized in Table 2. Among the 35 patients showing mutations, 17.2% (n=6) were homozygous, 5.7% (n=2) were compound heterozygous, and 77.1% (n=27) were heterozygous.

Compared to the BA and MA mutation groups, we found higher IgA levels in the BA group (1.5±0.7 vs 0.9±0.3 mg/dL, respectively, P=0.008). On the other hand, there was no significant difference between the mutation groups in terms of the mean levels of other quantitative immunoglobulins and IgE (P>0.05) (Table 3). An interesting finding was that all three patients with a homozygous M694 mutation had an IgA level above the upper limit.

Discussion

In this study, we aimed to detect a possible immune regulation imbalance in patients with FMF based on laboratory findings. We did not find an immunoglobulin deficiency or lymphopenia. However, our results showed higher IgA levels in the BA group compared to the MA group.

Autoinflammatory diseases result from inappropriate activation of antigen-independent inflammatory mechanisms [9]. Autoinflammation involves the interplay between the innate immune system—neutrophils, macrophages, and NK cells—and the adaptive immune system [10]. In this study, there was no significant difference between the levels of serum immunoglobulins IgA, IgM and IgG in the patient and control groups, which was in accordance with the study by Kholoussi et al. [11]. However, they did not compare serum Ig levels by mutation groups. To our knowledge, our study is the first to compare serum Ig levels by mutation groups.

As in the study by Kholoussi et al. [11], we did not find any difference in the mean ALC; however, Özer et al. [12] and Duksal et al. [13], unlike our study, reported higher lymphocyte counts in FMF patients than in healthy individuals.

Table 1. Comparison of demographic variables and immunological laboratial parameters in FMF patients and control group

Variables	No. (%)/Mean±SD		
	Case (N=35)	Control (N=20)	P
Gender (male)	9 (25.7)	13 (65)	0.004
Mean age (month)	127±53	103±57	0.113
Absolute lymphocytes count	3002±1230	3443±1177	0.204
Eosinophil number	211±41	263±52	0.445
Ig A (mg/ dL)	1.1±0.5	0.9±0.6	0.371
Ig G (mg/ dL)	9.8±2.0	8.6±3.1	0.133
Ig M (mg/ dL)	1.2±0.4	1.0±0.5	0.160
Ig E (mg/ dL)	40.0±9.1	50.5±9.4	0.431

Table 2. Distribution of MEFV genotypes in the study group.

Variables	Mutation (n=35)
M694V/M694V	5
M694V/V726A	1
M680I/M680I	1
M698V/R202Q	1
P369S/-	4
M694V/-	12
M680I/-	1
V726A/-	6
R202Q/-	2
A744S/-	2

Table 3: Comparison of immunologic laboratorial parameters between patients with biallelic and monoallelic mutations

Variable	Mean±SD		P
	Biallelic Mutation (n=8)	Monoallelic Mutation (n=27)	
Lymphocyte number	2748±832	3077±1329	0.410
Eosinophil number	238±139	203±36	0.812
Ig A (mg/ dL)	1.5±0.7	0.9±0.3	0.008*
Ig G (mg/ dL)	10.0±1.7	9.7±2.2	0.668
Ig M (mg/ dL)	1.3±0.3	1.1±0.4	0.329
Ig E (mg/ dL)	23.6±7.0	45.0±11.5	0.126

*P<0.05

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We found higher levels of IgA in patients with BA mutations compared to those with MA mutations. Moreover, three patients with IgA levels above the upper limit of normal had a homozygous *M694V* mutation. Previous studies have indicated that patients with homozygous or compound heterozygous mutations tend to have a more severe disease presentation compared to those with heterozygous mutations, especially those with homozygous *M694V* [14]. It is well-established that the incidence of Ig A vasculitis (IgAv) in FMF is 250-500 times higher than in the general population [15]. The association of IgAV with FMF, occurring at a frequency of 10%, was first reported by Flatau et al. in 1982 [16]. This finding has been extensively documented by several researchers [15, 17, 18]. IgA vasculitis is characterized by the accumulation of IgA1 in vessel walls, particularly affecting the skin, intestines, joints and kidneys [19]. There is a suggestion that a potential vasculitic process is associated with FMF, indicating that proinflammatory cytokines might induce endothelial cell dysfunction and injury, leukocyte infiltration, and fibrinoid necrosis in the arteries [20]. Ekinci et al. showed that the presence of *MEFV* variants on exon 10 was related to higher serum IgA levels compared to patients with *MEFV* variants in other exons (233.8±91 vs 1187.8±89.0 mg/dL; P=0.042) [21]. Gullu et al. presented a 56-year-old man diagnosed with IgA nephritis and FMF [22]. Genetic examination showed the homozygous M 694V/M694 V *MEFV* gene mutation. He had also high serum IgA levels. Rigante et al. and Said et al. present three patients diagnosed with FMF and Ig A nephropathy, all with high serum levels of IgA [23, 24]. Unfortunately, the mutations were not specified in these cases. Additionally, abdominal pain and intussusception are more frequently observed in patients with IgA vasculitis and *MEFV* variants in exon 10, suggesting that *MEFV* mutations in exon 10 may modulate the clinical presentation of HSP. In light of these discoveries, we anticipate that future studies will shed light on the connection between severe FMF mutations/clinical manifestations and elevated IgA levels, the underlying mechanism of which we have yet to elucidate [25-27].

Our study has some limitations. Firstly, it was partly retrospective in design; secondly, it involved a relatively small number of patients.

Conclusion

No significant difference was found in terms of humoral immunity between FMF patients and healthy individuals. We did not come across any study that identified such a difference either. However, we believe that IgA levels should be examined in patients with severe FMF manifestations, especially since the finding of high IgA levels in three patients with the homozygous *M694V* mutation supports our hypothesis. Although this data is not enough for a definitive conclusion, it may provide grounds for future studies. We propose that high IgA levels in a patient with IgAv and protracted abdominal pain may indicate a severe *MEFV* mutation. Therefore, further prospective studies are needed to confirm this hypothesis.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Ethics Committee of Kırıkkale University (Code: 2022.09.18, Date: 19.10.2022).

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Authors' contributions

All authors equally contributed to the preparation of this article.

Conflict of interest

The authors declared no conflict of interests.

References

[1] Sarı İ, Birlik M, Kasifoğlu T. Familial Mediterranean fever: An updated review. Eur J Rheumatol. 2014; 1(1):21-33. [DOI:10.5152/eurjrheum.2014.006] [PMID] [PMCID]

[2] Yüksel S, Ayvazyan L, Gasparyan AY. Familial Mediterranean fever as an emerging clinical model of atherogenesis associated with low-grade inflammation. Open Cardiovasc Med J. 2010; 4:51-6 [DOI:10.2174/1874192401004010051] [PMID] [PMCID]

[3] Fonnesu C, Cerquaglia C, Giovinale M, Curigliano V, Verrecchia E, de Socio G, et al. Familial Mediterranean fever: A review for clinical management. J Joint Bone Spine. 2009; 76(3):227-33. [DOI:10.1016/j.jbspin.2008.08.004] [PMID]

[4] Manna R, Cerquaglia C, Curigliano V, Fonnesu C, Giovinale M, Verrecchia E, et al. Clinical features of familial Mediterranean fever: An Italian overview. Eur Rev Med Pharmacol Sci. 2009; 13(Suppl 1):51-3. [PMID]

[5] Schroder K, Tschopp J. The inflammasomes. Cell. 2010; 140(6):821-32. [DOI:10.1016/j.cell.2010.01.040] [PMID]

[6] Vivier E, Raulet DH, Moretta A, Caligiuri MA, Zitvogel L, Lanier LL, et al. Innate or adaptive immunity? The example of natural killer cells. Science. 2011; 331(6013):44-9. [DOI:10.1126/science.1198687] [PMID] [PMCID]

[7] Chae JJ, Aksentijevich I, Kastner DL. Advances in the understanding of familial Mediterranean fever and possibilities for targeted therapy. Br J Haematol. 2009; 146(5):467-78. [DOI:10.1111/j.1365-2141.2009.07733.x] [PMID] [PMCID]

[8] Livneh A, Langevitz P. Diagnostic and treatment concerns in familial Mediterranean fever. Best Pract Res Clin Rheumatol. 2000; 14(3):477-98. [DOI:10.1053/berh.2000.0089]

[9] Wang DQH, Bonfrate L, de Bari O, Wang TY, Portincasa P. Familial Mediterranean fever: From pathogenesis to treatment. J Genet Syndr Gene Ther. 2014; 5:1-11. [Link]

[10] Schuetz C, Niehues T, Friedrich W, Schwarz K. Autoimmunity, autoinflammation and lymphoma in combined immunodeficiency (CID). Autoimmun Rev. 2010; 9(7):477-82. [DOI:10.1016/j.autrev.2010.02.005] [PMID]

[11] Kholoussi S, Kholoussi N, Zaki ME, El-Bassyouni HT, Elnady H, Morcos B, et al. Immunological evaluation in patients with familial Mediterranean fever. Open Access Maced J Med Sci. 2018; 6:310-3 [DOI:10.3889/oamjms.2018.079] [PMID] [PMCID]

[12] Özer S, Yılmaz R, Sönmezgöz E, Karaaslan E, Taşkın S, Bütün İ, et al. Simple markers for subclinical inflammation in patients with Familial Mediterranean Fever. Med Sci Monit. 2015; 21:298-303. [DOI:10.12659/MSM.892289] [PMID] [PMCID]

[13] Duksal F, Alaygut D, Güven AS, Ekici M, Oflaz MB, Tuncer R, et al. Neutrophil- lymphocyte ratio in children with familial Mediterranean fever. Eur J Rheumatol. 2015; 2(1):20-3. [DOI:10.5152/eurjrheumatol.2015.0093] [PMID] [PMCID]

[14] Güneş-Yılmaz S, Kasap-Demir B, Soyaltın E, Erfidan G, Özdemir-Şimşek Ö, Arslansoyu-Çamlar S, et al. Prediction of more severe MEFV gene mutations in childhood. Turk Arch Pediatr. 2021; 56(6):610-7. [DOI:10.5152/TurkArchPediatr.2021.21147] [PMID] [PMCID]

[15] Schlesinger M, Rubinow A, Vardy PA. Henoch-Schönlein purpura and familial Mediterranean fever. Isr J Med Sci. 1985; 21(1):83-5. [PMID]

[16] Flatau E, Kohn D, Schiller D, Lurie M, Levy E. Schönlein-Henoch syndrome in patients with familial Mediterranean fever. Arthritis Rheum. 1982; 25(1):42-7. [DOI:10.1002/art.1780250107] [PMID]

[17] Ozdogan H, Arisoy N, Kasapçapur O, Sever L, Calişkan S, Tuzuner N, et al. Vasculitis in familial Mediterranean fever. J Rheumatol. 1997; 24(2):323-7. [PMID]

[18] Tekin M, Yalçinkaya F, Tümer N, Akar N, Misirlioğlu M, Cakar N. Clinical, laboratory and molecular characteristics of children with Familial Mediterranean Fever-associated vasculitis. Acta Paediatr. 2000; 89(2):177-82. [PMID]

[19] Saulsbury FT. Clinical update: Henoch-Schönlein purpura. Lancet. 2007; 369(9566):976-8. [DOI:10.1016/S0140-6736(07)60474-7] [PMID]

[20] He X, Yu C, Zhao P, Ding Y, Liang X, Zhao Y, et al. The genetics of Henoch-Schönlein purpura: A systematic review and meta-analysis. Rheumatol Int.2013; 33(6):1387-95. [DOI:10.1007/s00296-012-2661-4] [PMID]

[21] Ekinci RMK, Balci S, Bisgin A, Atmis B, Dogruel D, Altintas DU, et al. MEFV gene variants in children with Henoch-Schönlein purpura and association with clinical manifestations: A single-center Mediterranean experience. Postgrad Med. 2019; 131(1):68-72. [DOI:10.1080/00325481.2019.1552479] [PMID]

[22] Gullu BE, Çelik S, Dagel T, Dogan İ, Kahvecioglu S , Durak H, et al. IgA Nephritis in a patient with familial Mediterranean Fever: 5 years-follow-up. Turkish J Nephrol. 2010; 19:224-7. [DOI:10.5262/tndt.2010.1003.15]

[23] Rigante D, Federico G, Ferrara P, Maggiano N, Avallone L, Pugliese AL, et al. IgA nephropathy in an Italian child with familial Mediterranean fever. Pediatr Nephrol. 2005; 20(11):1642-4. [DOI:10.1007/s00467-005-2023-5] [PMID]

[24] Said R, Nasrallah N, Hamzah Y, Tarawneh M, al-Khatib M. IgA nephropathy in patients with familial Mediterranean fever. Am J Nephrol. 1988; 8(5):417-20. [DOI:10.1159/000167628] [PMID]

[25] İlgen U, Nergizoğlu G. Less IgA deposits with more severe disease: The immunoclinical paradox in Henoch-Schönlein Purpura with MEFV mutations. Clin Rheumatol. 2019; 38(11):3311-3. [DOI:10.1007/s10067-019-04677-0] [PMID]

[26] Abbara S, Grateau G, Ducharme-Bénard S, Saadoun D, Georgin-Lavialle S. Association of vasculitis and familial Mediterranean fever. Front Immunol. 2019; 10:763. [DOI:10.3389/fimmu.2019.00763] [PMID] [PMCID]

[27] Chbihi M, Dumaine C, Deschênes G, Couderc A, Monteiro RC, Hogan J, et al. A pediatric case of IgA nephropathy associated with familial Mediterranean fever. Arch Clin Med Case Rep. 2020; 4:218-5. [DOI:10.26502/acmcr.96550189]