Northwestern Med J. 2023;3(2):74-80
doi: 10.54307/NWMJ.2023.38039

Original Article

Similarities and differences between familial Mediterranean fever (FMF) and multisystem inflammatory syndrome (MIS-C) in children

Çocuklarda ailevi Akdeniz ateşi (FMF) ve multisistem inflamatuar sendrom (MIS-C) arasındaki benzerlikler ve farklılıklar

Meyri Arzu Yoldaş, Aslı Çelebi Tayfur, Fatma Hancı, Ayşegül Danış, Semih Bolu, Halil İbrahim Atasoy

Atıf/Cite as: Yoldaş MA, Çelebi Tayfur A, Hancı F, Danış A, Bolu S, Atasoy Hİ. Similarities and differences between familial Mediterranean fever (FMF) and multisystem inflammatory syndrome (MIS-C) in children. Northwestern Med J. 2023;3(2):74-80.

ABSTRACT

Aim: We aimed to reveal the similarities and differences between the rare and severe multisystem inflammatory syndrome (MIS-C) and active familial Mediterranean fever (FMF) disease in children. Our study may help in the early recognition of MIS-C syndrome in children and distinguish it from other diseases with similar symptoms.
Methods: We evaluated the demographic and clinical characteristics, laboratory findings, treatments and outcomes of patients with MIS-C syndrome and active FMF.
Results: The clinical and laboratory findings of a total of 66 patients hospitalized in our pediatric clinic with the diagnosis of active FMF (n:42) and MIS-C syndrome (n:24) were reviewed retrospectively. The reason for pediatric emergency admission was determined as resistant fever in all patients. When the clinical findings of the patients were compared, it was determined that joint and abdominal pain in the FMF group and vomiting, rash, cough, Lenfadenopati (LAP) and myalgia findings in the MIS-C group were statistically significantly higher ($p<0.05$). When the laboratory findings were evaluated between the two groups, the lymphocyte count and vitamin D levels were statistically significantly lower, while the leukocyte count, glucose, C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), sedimentation, aspartate aminotransferase (AST), alanine aminotransferase (ALT) were found to be significantly higher in the group with MIS-C syndrome ($p<0.05$).
Conclusion: We think that the results of our study may guide pediatricians and clinicians in the early differential diagnosis and management of MIS-C, by showing the similarities and differences among MIS-C patients from autoinflammatory diseases such as FMF.

Keywords: COVID-19, Familial Mediterranean fever, SARS-CoV-2

ÖZ

Amaç: Çocuklarda nadir görülen ve şiddetli multisistem inflamatuar sendrom (MIS-C) ile aktif ailesel Akdeniz ateşi (FMF) hastalığı arasındaki benzerlik ve farklılıkları ortaya koymayı amaçladık. Çalışmamız, çocuklarda MIS-C sendromunun erken tanınmasına ve benzer semptomları olan diğer hastalıklardan ayırt edilmesine yardımcı olabilir.
Yöntem: MIS-C sendromlu ve aktif FMF'li hastaların demografik ve klinik özelliklerini, laboratuvar bulgularını, tedavilerini ve sonuçlarını değerlendirdik.
Bulgular: Çocuk kliniğimizde aktif FMF (n: 42) ve MIS-C sendromu (n: 24) tanısı ile yatırılan toplam 66 hastanın klinik ve laboratuvar bulguları retrospektif olarak incelendi. Pediatrik acil başvuru nedeni tüm hastalarda dirençli ateş olarak belirlendi. Hastaların klinik bulguları karşılaştırıldığında, FMF grubunda eklem ve karın ağrısı, MIS-C grubunda kusma, döküntü, öksürük, LAP ve miyalji bulgularının istatistiksel olarak anlamlı derecede yüksek olduğu belirlendi ($p<0.05$). İki grup arasında laboratuvar bulguları değerlendirildiğinde MIS-C sendromlu ($p<0.05$) grupta lenfosit sayısı ve D vitamini düzeyleri istatistiksel olarak

Received: 26.10.2022
Accepted: 24.04.2023
Publication date: 01.06.2023

Corresponding Author:
M. A. Yoldaş
ORCID: 0000-0003-0288-1529
Abant İzzet Baysal Training and Research Hospital, Department of Child Health and Diseases, Bolu, Türkiye
✉ m.arzuyoldas@gmail.com

A. Çelebi Tayfur
ORCID: 0000-0002-6280-4587

F. Hancı
ORCID: 0000-0002-1019-9207

A. Danış
ORCID: 0000-0003-0962-2116

S. Bolu
ORCID: 0000-0002-8183-2188

H. İ. Atasoy
ORCID: 0000-0003-1685-0352

Abant İzzet Baysal Training and Research Hospital, Department of Child Health and Diseases, Bolu, Türkiye

anlamlı derecede düşük bulunurken, lökosit sayısı, glukoz, C-reaktif protein (CRP), ferritin, laktat dehidrogenaz (LDH), sedimantasyon, aspartat transaminaz (AST) ve alanin aminotransferaz (ALT) anlamlı olarak yüksek bulundu.
Sonuç: Çalışmamızın sonuçlarının, MIS-C hastalarının FMF gibi otoinflamatuar hastalıklardan benzerliklerini ve farklılıklarını göstererek, MIS-C'nin erken ayırıcı tanısında ve yönetiminde pediatristlere ve klinisyenlere rehberlik edebileceğini düşünmekteyiz.

Anahtar kelimeler: Ailevi Akdeniz ateşi, COVID-19, SARS-CoV-2

INTRODUCTION

Recently, a severe syndrome called "multiple system inflammatory syndrome in children" (MIS-C), known to be associated with SARS-CoV-2 infection in children and adolescents, has been described (1). Multisystem Inflammatory Syndrome (MIS-C), a new phenomenon reported worldwide, has changed the notion of milder effects of COVID-19 infection in children. In light of recent information, MIS-C is accepted as a complication that can develop after active SARS-CoV-2 infection (2). Most affected children were found to be RT-PCR negative but antibody positive for the SARS-CoV-2 virus. Although the information on this subject is not certain, it has been assumed that there is a post-infection inflammatory response following SARS-CoV-2 infection (3). In children, it is characterized by treatment-resistant fever, multisystemic hyperinflammatory response, and multi-organ failure, beginning two to six weeks after the acute infection period. In addition, the similarity of this condition to previously well-defined inflammatory syndromes in children (such as Kawasaki disease, macrophage activation syndrome, and toxic shock syndrome) may make early diagnosis difficult (4). Familial Mediterranean fever (FMF), an autoinflammatory rheumatic disease, is characterized by recurrent attacks of fever, abdominal pain, and serositis, mostly seen in the Mediterranean basin. It is more common among Sephardic Jews, Armenians, Turks, and Arabs (4,5). Common features have been reported in laboratory findings and clinical symptoms of FMF and severe COVID-19 patients. The cytokine storm that occurs in the inflammatory period can also occur in autoinflammatory diseases. As a result of this hyperinflammatory response, symptoms such as recurrent fever, abdominal pain, and chest pain are not only specific to FMF disease, but may also occur in MIS-C patients (6-8).

The epidemiology, pathogenesis, and clinical spectrum of MIS-C are not yet fully known. It is very important to make a quick and early diagnosis, as it can often cause a critical and intensive care process in children. In this study, we aimed to reveal the similarities and differences between MIS-C and FMF disease. We think that our study will guide the early recognition of MIS-C syndrome in children and distinguish it from other diseases with similar symptoms and contribute to the literature.

MATERIAL and METHODS

Study population and design

Data from a total of 66 patients who were hospitalized in our pediatric clinic between March 2020 and February 2022 with the diagnosis of active FMF (n: 42) and MIS-C syndrome (n: 24) were obtained from hospital medical records and analyzed retrospectively. The reason for pediatric emergency admission was determined as resistant fever in all patients. All patients had a negative COVID-19 test by RT-PCR on nasopharyngeal (NP) swabs, and patients with chronic disease, immunodeficiency, malignant, infectious, or inflammatory disease and using glucocorticoids were excluded from the study. All MIS-C patients met the criteria recommended by the Center for Disease Control (CDC) and the World Health Organization (WHO) clinical case definition criteria (9,10). All of our MIS-C patients had a history of previous contact or transmission with COVID-19 patients. All patients followed up for MIS-C were given 2g/kg intravenous immunoglobulin and 50-80 mg/kg aspirin therapy. Pediatric patients diagnosed with FMF according to Livneh criteria

were included in the study (11). All active FMF patients were receiving colchicine treatment. The patients were divided into two groups: FMF patient group Group 1 (n:42) and MIS-C patient group Group 2 (n:24). Patients' demographic data such as age, gender, weight and height, systemic symptoms (such as fever, abdominal pain, arthralgia), abnormal physical examination findings and common laboratory values including Hb (hemoglobin), mean corpuscular volume (MCV), red cell distribution width (RDW), white blood cell (WBC), neutrophil and lymphocyte counts, platelet (PLT) and glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, lactate dehydrogenase (LDH), fibrinogen, ferritin, sedimentation, and C-reactive protein (CRP) levels were compared retrospectively.

Statistical analysis

Continuous data were expressed as mean ± SD (min-max), and categorical variables as frequency and percentage for each group. Various statistical tests were applied, depending on the data distribution. The Kolmogorov-Smirnov test was used to determine the normality of the variables. The independent samples t-test was applied to normally distributed variables, while Pearson's chi-square test and Fisher's exact test were applied to categorical variables. The results were assessed within a 95% confidence interval and at a significance level of $p < 0.05$. Analyses were performed using Statistical Package for Social Sciences 25.0 for Windows software (SPSS Inc., Chicago, Illinois, USA).

RESULT

The clinical and laboratory findings of Group 1 (n: 42) patients hospitalized with active FMF and Group 2 (n: 24) patients hospitalized with the diagnosis of MIS-C syndrome at the time of admission were compared. Of the patients, 39 (59.10%) were boys and 27 (40.90%) were girls. The mean age of the patients was 10.69±3.72 years in the FMF group and 9.45± 4.64 years in the MIS-C group. The two groups were compared

Table 1. Demographic and anthropometric characteristics of the groups.

		FMF Group (n:34)	MIS-C Group (n:17)	p
		Mean (±SD)	Mean (±SD)	
Gender, n* (%)	boy	20 (47,6%)	19 (79,2%)	0,19
	girl	22 (52,4%)	5 (20,8%)	
Age (year) **		10,69±3,72	9,45±4,64	0,24
Weight (kg) **		40,33±17,60	37,54±21,93	0,57
Height (cm) **		140,90±21,59	133,20±24,36	0,18

**The Pearson chi-square test was used in the analysis of categorical variables at two independent group analysis. **SD = standard deviation. Student's T-test was applied as the statistical technique, the results being expressed as mean (±standard deviation). FMF: Familial Mediterranean Fever, MIS-C: Multisystem Inflammatory Syndrome.*

Table 2. Clinical symptoms at presentation.

Symptoms	FMF Group (n:42)	MIS-C Group (n:24)	p
Abdominal pain	41(97,6%)	18(75,0%)	**0.004**
Vomiting	2(4,8%)	10(41,7%)	**<0.001**
Diarrhoea	4(9,5%)	5(20,8%)	0.19
Cough	0(0,0%)	7(29,2%)	**<0.001**
Headache	2(4,8%)	1(4,2%)	0,9
Arthralgia	29(69,0%)	5(20,8%)	**<0.001**
Rash	0(0,0%)	8(33,3%)	**<0.001**
Lymphadenopathy	3(7,1%)	7(29,2%)	**0.016**
Myalgia	2(4,8%)	12(50,0%)	**<0.001**

All data are Pearson's chi-square test was used. FMF: Familial Mediterranean Fever, MIS-C: Multisystem Inflammatory Syndrome.

in terms of demographic data. No statistically significant difference was observed between the groups in terms of age, gender, weight, and height (Table 1). All of the patients were found to have persistent fever and malaise at the time of admission to the pediatric emergency department. When the clinical findings were compared, abdominal pain (97.6%) and arthralgia (69.0%) were significantly higher in the FMF group, while rash (33.3%), cough (29.2%),

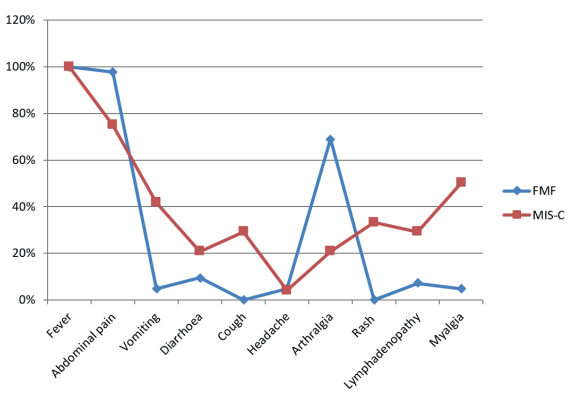

Figure 1. Clinical symptoms at presentation.

Table 3. Hematological variables in both groups.

Variables	FMF Group (n:42)	MIS-C Group (n:24)	P
WBC ($x10^3$/L)	6,82±2,79	11,9±7,59	<0.001
Neutrophils ($x10^3$/L)	4,70±9,68	5,81±5,16	0,6
Lymphocytes ($x10^3$/L)	2,95±2,15	1,93±1,39	0,041
Hemoglobin (g/dL)	13,20±1,26	12,71±1,75	0,19
MCV (fl)	80,80±4,73	80,25±4,07	0,69
RDW (%)	12,93±1,32	18,54±26,53	0,17
MPV (fl)	9,96±1,16	10,02±1,31	0,84
PLT ($x10^3$/L)	314,47±76,08	305,00±172,16	0,75

All data are mean±standard deviation. WBC: white blood cells, MCV: mean corpuscular volume, RDW: red cell volume distribution with, MPV: mean platelet volume, PLT: platelet, MIS-C: Multisystem Inflammatory Syndrome, FMF: Familial Mediterranean Fever.

Table 4. Comparison of biochemical parameters.

Biochemical parameters	FMF Group (n:42)	MIS-C Group (n:24)	P
Glucose (mg/dl)	92.2±11.5	105.2±30.3	0.015
Ferritin (ng/mL)	39,37±36,38	369,29±411,9	<0.001
CRP (mg/dl)	15,91±31,89	107,52±88,22	<0.001
Sedimentation (mm/h)	14,73± 10,01	41,87±37,28	<0.001
Fibrinogen (mg/dl)	332,66±98,75	354,58±339,06	0,69
LDH (U/L)	238,42±48,54	420,04±208,90	<0.001
AST (U/L)	25,52±18,56	76,70±92,09	0.001
ALT (U/L)	18,54±12,04	92,95±171,86	0.007
Urea (mg/dl)	24,42±12,77	25,04±18,67	0.87
Creatinine (mg/dl)	0,60±0,12	1,46±3,75	0,14
Vitamin D (µg/L)	17,64±9,56	7,80±8,24	<0.001
Vitamin B_{12}(ng/L)	334,76±109,4	221,9±262,9	0,17

All data are mean±standard deviation. CRP: C-reaktif protein, LDH: laktat dehidrogenaz, AST: aspartat transaminaz, ALT: alanin aminotransferaz, MIS-C: Multisystem Inflammatory Syndrome, FMF: Familial Mediterranean Fever.

LAP (29.2%), vomiting (41.7%), and myalgia (50%) were significantly higher in the MIS-C group (for all $p<0.05$) (Table 2, Figure 1). When laboratory findings were evaluated between both groups, lymphocyte count and vitamin D levels were statistically significantly lower in the MIS-C group, while CRP, ferritin, LDH, sedimentation, leukocytes, thrombocyte, AST and ALT were found to be significantly higher in this group ($p<0.05$). The comparison of hemogram and biochemical parameters of the two groups is presented in Tables 3 and 4.

DISCUSSION

In this study, we compared various clinical and laboratory parameters of children with MIS-C and active FMF. Significant differences were found in the MIS-C group compared to the FMF group in both clinical and laboratory findings. Clinical findings including myalgia (50%), vomiting (41.7%), rash (33.3%), cough (29.2%), and LAP (29.2%) and laboratory findings including glucose, ferritin, CRP, leukocyte, sedimentation, LDH, AST, and ALT levels were significantly higher, while lymphocyte count and vitamin D (25-OH D) levels were significantly lower in the MIS-C group. Whereas, abdominal pain (97.6%) and arthralgia (69.0%) findings were significantly higher in FMF patients. Although MIS-C has similar features to FMF in children, we found that the inflammatory response observed in MIS-C was much more severe. Clinical and laboratory features that are significantly higher in MIS-C patients may assist clinicians in rapid and early differential diagnosis and management of MIS-C.

In FMF patients, especially fever (99%), abdominal pain (87.3%) and arthralgia (32.6%) being more common, various clinical findings including vomiting (11.3%), rash (10.7%), headache (9.3%), and myalgia (6.5%) have been reported during the attack period (12). In our study, fever (100%), abdominal pain (97.6%), and arthralgia (69.0%) were frequently detected during admission to the emergency department in patients with active FMF, while lymphadenopathy (7.1%), diarrhea (9.5%), vomiting (4.8%), headache (4.8%), and myalgia (4.8%) findings were detected less frequently.

In a meta-analysis, a total of 600 patients with MIS-C syndrome were evaluated and the most common presentation was reported as fever (97%), followed by gastrointestinal symptoms (80%), skin rashes (60%), respiratory symptoms (39%), and less frequently arthralgia (5.5%) (13). It has been shown that fever (100%), gastrointestinal symptoms such as abdominal pain (34%) and vomiting (25%), and skin rashes

(42%) are common in patients with MIS-C who present with similar findings. Less commonly, cough and respiratory distress were reported in 4.5% and 9.6% of patients, respectively (2). In our study, fever (100%), abdominal pain (75%), myalgia (50%), vomiting (41.7%), rash (33.3%), and lymphadenopathy (29.2%) were frequently detected during admission to the emergency department in patients with MIS-C group, while diarrhea (20.8%), arthralgia (20.8%), and headache (4.2%) findings were detected less frequently.

Another study compared patients with and without MIS-C in children with acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. It was found that the frequency of fatigue (51%), headache (34%), myalgia (34%) and lymphadenopathy (20%) was higher in children followed for MIS-C syndrome compared to other patients. It has also been reported that children with MIS-C are five times more likely (73%) to be admitted to intensive care (14).

In a study conducted by Otar Yener et al.[15], when patients with systemic juvenile idiopathic arthritis (sJIA-MAS), Kawasaki, and MIS-C were examined, gastrointestinal symptoms (72.7%) and myalgia (39.6%) were more common in MIS-C patients, while arthritis was recorded more commonly in sJIA- MAS patients than in others. In our study, in accordance with the literature, we found that, among clinical findings, LAP was significantly higher in patients with MIS-C than in patients with FMF. We showed that abdominal pain and joint pain were significantly more common in FMF patients, and vomiting, cough, skin rash, and myalgia symptoms were significantly higher in MIS-C patients. Arthritis was not observed in any of our patients. In the MIS-C patient group, cardiovascular support (fluid resuscitation and/or inotropic support) was required in one patient and tertiary intensive care was required in three patients. When the clinical findings were compared between the groups, fever and malaise found in all of our patients caused difficulties in the differential diagnosis. Significantly higher rates of vomiting, myalgia, cough, and rash in MIS-C patients may guide clinicians in early diagnosis.

High inflammatory markers can be seen in both MIS-C and rheumatic diseases (16-18). Studies have reported that elevated AST, ALT, CRP, erythrocyte sedimentation rate, D-dimer, LDH, fibrinogen, ferritin, white cell count, and lymphopenia among laboratory findings can be commonly encountered in patients with MIS-C syndrome (19-21). Today, the similarities of the findings of Kawasaki disease, MAS and toxic shock, MIS-C syndrome, and other hyperinflammatory syndromes in children are important, and it has become necessary to distinguish them quickly (22).

In the study of Rodriguez-Smith et al.[23], patients with MIS-C syndrome and disease with similar features, such as Kawasaki disease, systemic JIA, and MAS, were examined, and significant lymphopenia and high inflammatory markers were detected, and hyperferritinemia was observed in patients with MIS-C. While platelet counts during hospitalization were within normal limits for patients with MIS-C, they were found to be high in patients with Kawasaki disease. In our study, we found significantly higher ferritin, CRP, leukocyte count, erythrocyte sedimantation rate, LDH, AST, and ALT values in MIS-C patients, in accordance with the literature. We did not find a significant difference between the platelet counts when the two groups were compared. It is known that MIS-C syndrome can often have a serious course in children and should be followed closely. Although not diabetic, hyperglycemia is a common complication in critically ill children. Insulin resistance (IR) that may occur in these cases may be due to dysregulation of glucose metabolism relative insulin deficiency in response to the stress reaction that develops in the body.

In a study, it was determined that IR, glycemic fluctuations, and/or hyperglycemia may occur in 30 normal-weight pediatric patients affected

by MIS-C without glycemic disorder. The mean blood glucose level of the patients followed up due to MIS-C was 105 mg/dL (24).

In our study, we found that the glucose level in the MIS-C group was 105.2 mg/dL (±30.3 mg/dL SD), and it was significantly higher than the FMF group. This suggests that MIS-C syndrome may have triggered mechanisms that may result in mild to moderate hyperglycemia driven by hormones and cytokines related to stress conditions in the body, as it has a severe course and causes a critical condition.

Vitamin D (25-OH D) can reduce the risk of infection through several mechanisms, such as reducing viral replication rates and concentrations of pro-inflammatory cytokines and increasing concentrations of anti-inflammatory cytokines (25). A negative correlation was observed between the mean vitamin D (25-OH D) levels and COVID-19 infection (26). It is thought that vitamin D may be effective in predicting severe forms of MIS-C due to its immunomodulatory functions and supplementation of 25-hydroxyvitamin D3 (25-OH D3) may be effective in reducing the severity of MIS-C (27).

In our study, we found that vitamin D (25-OH) levels were significantly lower in the MIS-C group. Depending on the severity of MIS-C, this may lead to the formation of a hyper-inflammatory process, an increase in the need for vitamin D, which has an anti-inflammatory role, and a decrease in the level of vitamin D in the serum. It has not been determined whether vitamin D levels can be used as a biomarker for the severity of MIS-C in clinical practice, and more studies are needed on this subject.

This study has some limitations. Since our study was conducted in a single center, we could not estimate the possibility of potential risk factors for the disease due to ethnicity and socioeconomic status. In addition, IL-6 and D-dimer, which are among the laboratory findings of severe inflammation, could not be evaluated due to the lack of results.

CONCLUSION

Determining the similarities and differences in clinical and laboratory findings between MIS-C and active FMF will facilitate the emergency approach of MIS-C in children and will help in the differential diagnosis of MIS-C from other inflammatory conditions.

Ethics Committee Approval: The study protocol was approved by the Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (26.04.2022 / 2022/119).

Conflict of Interest: The authors have declared that they have no conflict of interest.

Funding: The authors have declared that they have not received any financial support.

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