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Research

Is There an Association Between Initial Clinical Manifestations and the Development of Macrophage Activation Syndrome in Patients with Systemic Juvenile Idiopathic Arthritis?

Sistemik Jüvenil İdiyopatik Artritin Klinik Prezentasyonuyla Makrofaj Aktivasyon Sendromu Gelişimi Arasında İlişki Var Mı?

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ABSTRACT

Objective: Systemic juvenile idiopathic arthritis is deemed as a subtype of the disease complex known as juvenile idiopathic arthritis but differs in the point of its clinical manifestations and pathophysiological features. Besides, macrophage activation syndrome is a potentially fatal complication of systemic juvenile idiopathic arthritis requiring timely management. The study aims to evaluate the presence and recurrence of macrophage activation syndrome according to the initial symptoms and pattern of different phenotypes in systemic juvenile idiopathic arthritis to reveal the comprehensive association of these interrelated disorders.

Methods: The study was conducted at the Department of Pediatric Rheumatology in Istanbul University, Istanbul Faculty of Medicine with a retrospective design, covering the date range 2015 to 2021. Patients, aged 0-18 years, being followed up with a diagnosis of systemic juvenile idiopathic arthritis with or without macrophage activation syndrome were enrolled in the study. The details of demographic data and disease-related clinical and laboratory information were investigated both from their records and the hospital database. The patients with missing or insufficient data and without regular follow-up were excluded from the study.

Results: Seventy-eight patients followed up with the diagnosis of systemic juvenile idiopathic arthritis were included in the study. The gender distribution in the study was equivalent randomly (F/M: 39/39). The median age at the study was 174 (29-229) months. The development and recurrence of macrophage activation syndrome revealed statistical significance between the genders; p=0.01 and p=0.02 respectively. Macrophage activation syndrome was more common in patients with evanescent rash (p=0.00) and those without arthritis (p=0.01). The development of macrophage activation syndrome was statistically higher in patients with predominant systemic symptoms (p=0.02) and polyphasic course (p=0.01). The presence of serositis (p=0.01) correlated with the recurrent macrophage activation syndrome.

Conclusion: The results from our study were consistent in revealing the association between macrophage activation syndrome and the systemic features in systemic juvenile idiopathic arthritis, despite a lack of correlation with arthritis in the initial presentation of the disease. Early clinical indicators and comprehensive studies are required to predict the development of macrophage activation syndrome.

Keywords: Arthritis, child health and disease, emergency medicine, juvenile idiopathic arthritis, macrophage activation syndrome, pediatric rheumatology, systemic juvenile idiopathic arthritis

ÖZ

Amaç: Sistemik jüvenil idiyopatik artrit, jüvenil idiyopatik artrit olarak bilinen hastalık kompleksinin bir alt tipi olarak kabul edilir ancak klinik bulguları ve patofizyolojik özellikleriyle diğer alt tiplerden farklılık gösterir. Ayrıca makrofaj aktivasyon sendromu, sistemik jüvenil idiyopatik artritin zamanında tedavi gerektiren mortalitesi yüksek bir komplikasyonudur. Çalışmanın amacı, sistemik jüvenil idiyopatik artritte karşımıza çıkan farklı fenotiplerin başlangıç semptomlarına ve patternine göre makrofaj aktivasyon sendromunun varlığını ve rekürrensini değerlendirmek ve birbiriyle ilişkili bu bozuklukların kapsamlı birlikteliğini ortaya çıkarmaktır.

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Gereç ve Yöntem: Çalışma, İstanbul Üniversitesi, İstanbul Tıp Fakültesi Pediatrik Romatoloji Bilim Dalı'nda 2015-2021 tarih aralığını kapsayacak şekilde retrospektif olarak gerçekleştirildi. Makrofaj aktivasyon sendromu geçirmiş veya geçirmemiş sistemik jüvenil idiyopatik artrit tanısıyla izlenen 0-18 yaş arası hastalar çalışmaya alındı. Demografik verilerin detayları ve hastalıkla ilgili klinik ve laboratuvar bilgileri hem kendi kayıtlarından hem de hastane veri tabanından araştırıldı. Eksik veya yetersiz verisi olan ve düzenli takibi olmayan hastalar çalışma dışı bırakıldı.

Bulgular: Sistemik jüvenil idiyopatik artrit tanısıyla izlenen 78 hasta çalışmaya dahil edildi. Çalışmadaki cinsiyet dağılımı rastgele olarak eşitti (K/E: 39/39). Çalışmadaki ortanca yaş değeri 174 (29-229) ay olarak saptandı. Makrofaj aktivasyon sendromu gelişimi ve rekürrensi cinsiyetler arasında istatistiksel bir anlam göstermekteydi; sırasıyla p=0,01 ve p=0,02. Makrofaj aktivasyon sendromu, geçici döküntüsü olan hastalarda (p=0,00) ve artriti olmayanlarda (p=0,01) daha yaygındı. Sistemik semptomları baskın (p=0,02) ve polifazik seyirli (p=0,01) hastalarda makrofaj aktivasyon sendromu gelişimi istatistiksel olarak daha yüksekti. Serozit varlığı (p=0,01) tekrarlayan makrofaj aktivasyon sendromuyla korelasyon gösterdi.

Sonuç: Makrofaj aktivasyon sendromu sistemik jüvenil idiyopatik artritin geliş tablosunda yer alabilen artrit ile korelasyon göstermezken, sistemik özelliklerle arasındaki ilişki çalışma sonuçlarına göre tutarlıydı. Multidisipliner yaklaşım, yakın klinik izlem ve laboratuvar parametrelerinin seri ölçümü yönlendirici olabilmektedir, ancak göreceli değişiklikleri tespit etmek zordur. Bu nedenle, makrofaj aktivasyon sendromunun gelişimini öngörmek için erken klinik göstergelere ve kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Artrit, çocuk sağlığı ve hastalıkları, acil tıp, jüvenil idiyopatik artrit, makrofaj aktivasyon sendromu, pediatrik romatoloji, sistemik jüvenil idiyopatik artrit

INTRODUCTION

Systemic juvenile idiopathic arthritis (JIA) is deemed as a subtype of the disease complex known as JIA but differs in the point of its clinical manifestations and pathophysiological features (1). Systemic JIA deserves a rigorous distinction from infectious diseases and malignancy beyond the other autoimmune and autoinflammatory systemic disorders (2). However, the clinical picture may remain partial and challenging without a typical presentation. However, macrophage activation syndrome (MAS) is a potentially fatal complication of systemic JIA with a course of coagulopathy, haemodynamic instability, and multiorgan dysfunction, requiring timely management (3). In systemic JIA patients, leukocytosis, thrombocytosis, elevated sedimentation, and fibrinogen may mask the development of MAS (2). Considering the exacerbations of the underlying disease and the overlapping features with sepsis, MAS may render the picture more challenging to recognize.

Systemic JIA represents a heterogeneous portrait in which systemic features are predominant or arthritis is at the forefront, with variations in itself (4-6). It is difficult to foresee the course of the disease as it may display a monophasic, polyphasic, or persistent course (7). Monophasic and polyphasic courses may not always be accompanied by arthritis, and this group of patients may predominantly present with systemic symptoms similar to those seen in MAS, such as fever, rash, organomegaly, and generalized lymphadenopathy. However, MAS, which is estimated to occur in 10% of patients, may emerge at diagnosis, during an exacerbation of systemic JIA, or, conversely, when the disease is in remission (1). Although immune variances and genetic influences in the pathogenesis have been associated with clinical heterogeneity of systemic JIA, mechanistic differences between phenotypes have not been fully demonstrated. Moreover, it is a matter of debate whether MAS is a variant of the disease or a subtype presenting with a noisy clinic or subclinical course (3).

The current study evaluates the presence and recurrence of MAS according to the initial symptoms and pattern of different phenotypes in systemic JIA to reveal the comprehensive association of these two interrelated disorders.

METHODS

Patient Selection

The study was conducted with the patients being followed up with a diagnosis of systemic JIA at the Pediatric Rheumatology Department in Istanbul University, Istanbul Faculty of Medicine. The systemic JIA cohort composed of patients aged 0-16 years, who met the ILAR criteria (8) and who presented with disease features and were eventually diagnosed as systemic JIA after being eliminated from other possible etiologies with a multidisciplinary approach. The cohort included patients with or without MAS, which has been defined according to the 2016 classification criteria set (9). Special attention has been given to include patients who were diagnosed after excluding all existing causes, and without any signs that would raise the diagnostic suspicion during the follow-up and treatment processes.

Data Collection

Medical records covering the date range from September 1, 2015, to September 1, 2021, were retrospectively reviewed. The details of clinical and laboratory characteristics, demographic (age, gender) and disease-related (age at diagnosis, disease duration from the diagnosis to the time of the study, disease pattern, detailed history of symptoms, medication history, current treatment) data were assessed. Baseline laboratory data including leukocyte count, neutrophil percentage, platelet count, C-reactive protein, erythrocyte sedimentation rate, initial, maximum and the latest values of ferritin, alanine transaminase, aspartate transaminase, triglyceride, fibrinogen was investigated both

from their own records and from the hospital database. The patients with missing or insufficient data and without regular follow-up were excluded from the study. Each participant and his/her legal representative have approved the use of their information and informed consent was obtained from the legally authorized representatives of our patients before their inclusion in the study. Approval was obtained from the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine for the study (decision no: 622975, date: 25.11.2021).

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows 21.0 software (Statistical Package for the Social Sciences, Chicago, IL, USA) and Microsoft Excel (Redmond, WA). The visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) were performed to analyze the distribution of the variables. The demographic and clinical data were evaluated using descriptive analysis, and the data are presented as a percentage (%), median with minimum and maximum values. In the comparison and assessment of the data, non-parametric tests, Mann Whitney U and Kruskal-Wallis tests, were performed. Categorical variables were presented as counts or frequencies and Pearson chi-square, Fisher's Exact tests were performed to evaluate the correlations and differences. Statistical significance was defined as p-value <0.05.

RESULTS

Seven patients were excluded from the study because of missing or insufficient data, while 78 patients with a diagnosis of systemic JIA with or without MAS were enrolled. The number of female (F) and male (M) patients who met the inclusion criteria and randomly included in the cohort was equivalent (F/M: 39/39). The median age at the study was 174 (29-229) months. Among the patients in the cohort, 39.7% (n=31) had a history of clinically and laboratory-proven MAS in which 14.1% (n=11) were recurrent. Clinical characteristics of the patients in the cohort are demonstrated in Table 1.

The development and recurrence of MAS revealed statistical significance between the genders; (F/M: 10/21, p=0.01) and (F/M: 2/9, p=0.02) respectively. According to the initial presentation, MAS was more common in patients with evanescent rash (p=0.00) and in those without arthritis (p=0.01). Moreover, it was observed that the development of MAS was statistically higher in patients with systemic type of disease (p=0.02) and polyphasic course (p=0.01). In systemic JIA patients, lymphadenopathy and organomegaly were significant in terms of MAS development, whereas

Table 1. Clinical manifestations of the systemic juvenile idiopathic arthritis cohort

Characteristics med (min-max)/n (%)	Systemic JIA (n=78)
Gender (female)	39 (50)
Age at the study (mo)	174 (29-229)
Disease presentation	
Age at diagnosis (mo)	73 (6-180)
Fever	77 (98.7)
Evanescent erythematous rash	52 (66.7)
Arthralgia (≥2 weeks)	74 (94.9)
Arthritis at diagnosis	59 (75.6)
Type of arthritis	
Monoarthritis	14 (17.9)
Oligoarthritis	26 (33.3)
Polyarthritis	26 (33.3)
Major joint involvement	63 (80.8)
Minor joint involvement	14 (17.9)
Axial involvement	18 (23.1)
Generalized lymphadenopathy	22 (28.2)
Hepatomegaly and/or splenomegaly	32 (41)
Serositis	23 (29.5)
Baseline laboratory data	
WBC (x10^9/L)	17.4 (3.4-29)
Neutrophils	14.4 (2-24.6)
Platelet count (x10^9/L)	494 (110-963)
CRP (mg/L)	130 (28-388)
ESR (mm/h)	76 (12-140)
ALT (units/L)	32 (5-2,356)
AST (units/L)	38 (7-8,754)
Triglyceride (mg/dL)	121 (63-722)
Fibrinogen (mg/dL)	325 (122-822)
Ferritin (initial) (µg/L)	1133 (118-67,873)
Ferritin (maximum) Ferritin (latest)	2340 (310-115,000) 40 (10-235)
Clinical progress	
Disease duration (mo)	66 (25-190)
Disease course	
Monophasic	22 (28.2)
Polyphasic	21 (26.9)
Persistent	35 (44.9)
MAS	31 (39.7)

Table 1. Continiued

Characteristics med (min-max)/n (%)	Systemic JIA (n=78)
Recurrent MAS	11 (14.1)
Organ involvement	
CNS	6 (7.7)
Liver	15 (19.2)
Coronary	1 (1.3)
Kidney	3 (3.8)
ARDS	8 (10.2)
Intensive care unit follow-up	19 (24.4)
Mortality rate	0
Medication history [type, duration (mo)]	
High dose corticosteroid therapy	75 (96.2)
Methotrexate	54 (69.2), 17.5 (4-108)
Cyclosporine	31 (39.7), 3 (1-30)
Anakinra	33 (42.3), 4 (1-20)
Canakinumab	17 (21.8), 16 (3-56)
Tocilizumab	29 (37.2), 20 (1-70)
Etanercept	11 (14.1), 12 (3-36)
Adalimumab	3 (3.8), 6 (6-36)
Current treatment	
Methotrexate	3 (3.8)
Canakinumab	14 (17.9)
Tocilizumab	18 (23.1)
Etanercept	2 (2.6)
Oral corticosteroid	3 (3.8)
Medication-free	43 (55.1)

JIA: Juvenile idiopathic arthritis, WBC: White blood cell, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ALT: Alanine transaminase, AST: Aspartate transaminase, MAS: Macrophage activation syndrome, CNS: Central nervous system, ARDS: Acute respiratory distress syndrome med: Median

the presence of serositis correlated with MAS recurrence (p=0.01). The correlation between the demographic and clinical characteristics of the systemic JIA cohort and the development and recurrence of MAS is detailed in Table 2 with p-values.

Table 2. The correlation between demographic and clinical manifestations of the systemic juvenile idiopathic arthritis cohort and macrophage activation syndrome

Systemic JIA cohort	The development of MAS p-value	Recurrent MAS p-value
Demographic and clinical manifestations		
Gender	**0.01**	**0.02**
Age at diagnosis	0.47	0.9
Fever	1.0	1.0
Evanescent rash	**0.00**	0.08
Arthralgia (≥2 weeks)	0.14	1.0
Arthritis at diagnosis	**0.01**	0.44
Type of arthritis	0.3	0.29
Major joint	**0.01**	0.43
Minor joint	0.79	0.67
Axial involvement	0.93	1.0
Lymphadenopathy	**0.007**	0.27
Organomegaly	**0.001**	0.18
Serositis	0.14	**0.013**
CRP (mg/L)	0.56	0.64
ESR (mm/h)	**0.02**	0.05
Ferritin (initial)	**0.00**	**0.001**
Clinical progress		
Disease duration	**0.02**	0.26
Disease course	**0.01**	0.4
Disease type	**0.02**	0.28

JIA: Juvenile idiopathic arthritis, MAS: Macrophage activation syndrome, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

DISCUSSION

The study aimed to evaluate the presence and recurrence of MAS in systemic JIA and to determine whether the initial symptoms or patterns of different phenotypes demonstrate any association. MAS is known as a rare but life-threatening condition with high mortality (8%) (10). Although the prevalence of MAS in systemic JIA has been reported to be approximately 10% (11), recent data emphasize that it can be detected subclinical in 30-40% of patients (12). In a database study on systemic JIA conducted in Germany, the frequency of MAS was 5% (13). The rate may differ in studies from different centers but from the same geography. In the cohort of Barut et al. (14) consisting of 168 patients, the frequency of MAS was 11.9% with a value close to the expected. According to the results reported by another reference center in Turkey, 36% of the patients had at least one MAS episode during the disease (15). The results of our study in terms of the sample size and the frequency of MAS with many 39.7% were consistent with the aforementioned study. It is crucial to act consciously

and to refer patients to reference centers timely in order to prevent mortality. Hence, it must identify the clinical features and laboratory data that may not be included or may not display major alterations in the presentation.

MAS emerges because of cytolytic pathway defects resulting in sustained activation of CD8+ T-cells and macrophages and uncontrolled production of pro-inflammatory cytokines such as interferon-ɣ (IFN-ɣ) (16,17). IL-18 is principally thought to play a key role in the pathogenesis of systemic JIA, and in MAS by stimulating IFN-ɣ production (3,18). The fact that MAS may display either a subclinical course or recurrent episodes with prompt mortality is a subject of debate open to research. While no mortality was observed in the study cohort, recurrence has been noted in 14.1%. Our patients with recurrent MAS were evaluated for primary hemophagocytic lymphohistiocytosis (HLH) and possible genetic causes. Recent literature has pointed that inflammasome NLR-family CARD domain-containing protein 4 related mutations may lead to persistently elevated IL-18 levels and recurrent episodes of MAS (19,20). Further studies are needed to predict the course of MAS and to elucidate its pathophysiological and genetic aspects.

HLH-2004 diagnostic criteria presented for HLH were formerly used in a treatment study that evaluated the efficacy of etoposide, dexamethasone, and cyclosporine-based induction therapy before hematopoietic stem cell transplantation (21). The histopathological similarity between MAS and HLH suggested that common diagnostic criteria might be applied. However, more sensitive criteria were required to distinguish MAS from certain confounding conditions (22). In 2016, Ravelli et al. (9), and colleagues revealed classification criteria for systemic JIA-related MAS to differentiate MAS, particularly from the disease flare or infection. Of note, it is sufficient to suspect without waiting for all criteria to be met to start treatment. High ferritin levels and a relative decrease in platelet count are noted to be the essential flags for the diagnosis. Moreover, persistent fever, development of cytopenia and decrease in sedimentation value are the significant markers (3). When the initial symptoms and the disease course of systemic JIA were evaluated regarding the development of MAS, the presence of evanescent rash, lymphadenopathy and organomegaly came into prominence. Although the cutaneous signs in systemic JIA and MAS have distinct characteristics, MAS displayed a significant correlation with the evanescent rash of systemic JIA. However, it displayed an inverse correlation with arthritis at disease onset. Consequently, the systemic signs and the polyphasic course of systemic JIA were more associated with the development of MAS.

Unlike other JIA subtypes, no dominance is expected in terms of gender distribution in systemic JIA, and the distribution was equal in our study. However, although there is female predominance in some studies in terms of MAS (10,23,24), both the development and recurrence of MAS was statistically higher in male patients in our study. Patient populations and geographic diversity in different studies may be determinants of the demographic changes. Studies with a large multinational cohort are needed.

One downside regarding our methodology is that the study was conducted retrospectively with a limited sample size and data. As there are individual, ethnic, and temporal determinants, it is not easy to establish a direct correlation and predict the progression. However, the results from our study were consistent in revealing the association of MAS with the systemic shared features of systemic JIA, despite a lack of correlation with arthritis in the initial presentation of the disease.

CONCLUSION

Systemic JIA and MAS are heterogeneous conditions with consecutive and overlapping features. Given that early diagnosis and prompt management are of vital importance to prevent morbidity and mortality, it is crucial to have particular clinical indications that may be noticed early in the disease. The results from our study were consistent in revealing the association between the development and recurrence of MAS and the systemic features, despite a lack of correlation arthritis in systemic JIA. A multidisciplinary approach, close clinical monitorization, and serial measuring of laboratory parameters may be instructive, yet relative alterations may be difficult to detect. Studies on the pathways and triggers associated with cytokine storm will shed light on a deep understanding of the disease and treatment approaches. Besides, there is need for tools or clinical indicators that can be applied in practice, and which may guide clinicians in initial diagnosis and differential diagnosis.

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ETHICS

Ethics Committee Approval: Approval was obtained from the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine for the study (decision no: 622975, date: 25.11.2021).

Informed Consent: Each participant and his/her legal representative have approved the use of their information

and informed consent was obtained from the legally authorized representatives of our patients before their inclusion in the study.

Authorship Contributions

Surgical and Medical Practices: O.K., N.A.A., Concept: O.K., N.A.A., Design: O.K., N.A.A., Data Collection or Processing: O.K., N.A.A., Analysis or Interpretation: O.K., N.A.A., Literature Search: O.K., N.A.A., Writing: O.K., N.A.A.

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