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Systemic Juvenile Idiopathic Arthritis: A Diagnostic Challenge in Fever of Unknown Origin

Nedeni Bilinmeyen Ateşte Tanısal Bir Zorluk: Sistemik Jüvenil İdiyopatik Artrit

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Abstract

Objective: Fever of unknown origin (FUO) in children is a challenging diagnostic and management dilemma. Systemic juvenile idiopathic arthritis (sJIA) is an important cause of FUO in this population. This study aimed to investigate the characteristics of children with FUO that were ultimately diagnosed with sJIA arthritis.

Material and Methods: A retrospective analysis was performed on the medical records of 17 children with FUO that were later diagnosed with sJIA.

Results: Median age of the patients was six years, and 35.2% were female. The most common complaints were fever (100%), rash (94.11%), arthritis (70.58%), arthralgia (64.70%), intra-articular effusion (35.29%), hepatomegaly (47.05%), splenomegaly (41.17%), and lymphadenopathy (64.70%). Median duration of fever was 16 (11-50) days. Before admission, 70.58% of patients had seen a physician at least once, 55.80% had received empirical antibiotics, and 41.17% had received antihistamines. All patients were previously healthy, and only one had a family history of juvenile rheumatoid arthritis. Laboratory findings included leukocytosis (76.47%), elevated C-reactive protein (100%) and erythrocyte sedimentation rate (100%), hyperferritinemia (100%), and positive antinuclear antibody (64.70%). Treatment regimens included pulse steroids (nine patients), ibuprofen (eight patients), methotrexate (nine patients), low-dose steroids (two patients), and interleukin-1 antagonists (two patients).

Conclusion: sJIA should always be considered in the differential diagnosis of prolonged fever in children. Early diagnosis and treatment can improve prognosis and avoid antibiotic misuse.

Keywords: Fever of unknown origin, systemic juvenile idiopathic arthritis, children, clinical findings, laboratory findings

Öz

Giriş: Çocuklarda nedeni bilinmeyen ateş (NBA), zorlu bir tanı ve tedavi ikilemidir. Sistemik jüvenil idiyopatik artrit (sJİA), bu popülasyonda NBA'nın önemli bir nedenidir. Çalışmamızda NBA'sı olan ve sJİA tanısı konulan çocukların özelliklerini göstermeyi amaçladık.

Gereç ve Yöntemler: Nedeni bilinmeyen ateş ile tetkik edilen ve sonrasında sJİA tanısı konulan 17 çocuk hasta retrospektif olarak değerlendirildi.

Bulgular: Hastaların ortanca yaşı altı ve %35.2'si kız idi. En sık görülen şikayetler ateş (%100), döküntü (%94.11), artrit (%70.58), artralji (%64.70), eklem içi efüzyon (%35.29), hepatomegali (%47.05), splenomegali (%41.17) ve lenfadenopati (%64.70) idi. Ateşin ortanca süresi 16 (11-50) gündü. Hastaların %70.58'i başvurudan önce en az bir kez doktora başvurmuş, %55.80'i ampirik antibiyotik ve %41.17'si antihistaminik kullanmıştı. Hastaların tamamı önceden sağlıklıydı ve yalnızca bir hastanın ailesinde juvenil romatoid artrit öyküsü vardı. Laboratuvar bulguları; lökositoz (%76.47), yüksek C-reaktif protein (%100), eritrosit sedimentasyon hızı (%100), hiperferritinemi (%100) ve pozitif antinükleer antikor (%64.70) olarak saptandı. Pulse steroid (dokuz hasta), ibuprofen (sekiz hasta), metotreksat (dokuz hasta), düşük doz steroid (iki hasta) ve interlökin-1 antagonisti (iki hasta) tedavileri verildi.

Sonuç: Çocuklarda uzamış ateşin ayırıcı tanısında sJİA artrit her zaman akılda tutulmalıdır. Erken tanı ve tedavi prognozu iyileştirebilir ve antibiyotiklerin kötüye kullanımını önleyebilir.

Anahtar Kelimeler: Nedeni bilinmeyen ateş, sistemik jüvenil idiyopatik artrit, çocuk, klinik bulgular, laboratuvar bulguları

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Introduction

Fever of unknown origin (FUO) is characterized by recurrent temperature greater than 38.3°C (101°F) on several occasions, over three weeks, with no identifiable cause after one week of inpatient investigation (1). It is a complex diagnostic dilemma, with over 200 potential triggers, including infections, inflammatory diseases, malignancies, and other disorders (2). Diagnosis is based on comprehensive history, physical examination, and complementary testing. Empirical treatment is not recommended, as it can obscure the underlying disease, delay diagnosis, and prevent specific therapy (3). FUO is particularly challenging in children, and its differential diagnosis includes systemic juvenile idiopathic arthritis (sJIA), an autoinflammatory syndrome that can be difficult to distinguish from severe systemic infections (4).

JIA stands as the most prevalent chronic rheumatic disease affecting children, and its exact cause remains unknown. It is categorized into subgroups based on various factors, including demographics, clinical characteristics, treatment approaches, and prognosis (5). One such subgroup is sJIA, often characterized by inflammatory symptoms such as fever, arthritis, rash, generalized lymphadenopathy, hepatosplenomegaly, and serositis (6). In order to establish a diagnosis of sJIA, other potential causes, including infections, malignancies, and other rheumatic diseases, must be ruled out, as there is no single definitive diagnostic finding for sJIA. The pathogenesis is believed to involve a combination of immunological predisposition and environmental factors (7). sJIA typically follows a chronic course, marked by periods of exacerbations and remissions. Over the years, significant progress has been made in the treatment of sJIA. Therapeutic options include non-steroidal anti-inflammatory drugs, intraarticular corticosteroid injections, methotrexate, and biological agents, all of which have led to improved outcomes for children. Biological agents have proven both safe and effective in managing more severe forms of arthritis and associated conditions like uveitis (8).

Our study aimed to assess the clinical and laboratory parameters of children who were initially examined at our hospital due to FUO and subsequently diagnosed with sJIA during their follow-up period.

Materials and Methods

A retrospective evaluation was conducted on a total of 17 patients who were initially followed-up for FUO in the pediatric infection service and subsequently diagnosed with sJIA based on the International League Against Rheumatism criteria. The assessment covered the period from January 2018 to December 2019. During this analysis, information regarding patients' initial complaints upon admission, physical examination findings, laboratory parameters, and the treatment modalities employed were recorded. This study was performed in line with the principles of the Declaration of Helsinki. The study received approval from the Local Ethics Committee (Approval no: 2020/28-43).

Results

During the study, 212 patients were examined with FUO. Seventeen of 212 patients who were diagnosed with sJIA were included in the study. The remaining 20% of the patients followed with hematological malignancy, and 54% with infectious diseases. Median age of the 17 patients (six females and 11 males) diagnosed with sJIA was six years (ranging from nine months to 14 years). Among these patients, 70.58% had previously sought medical attention due to symptoms such as rash or fever but had not received a definitive diagnosis. About 55.80% of the patients had been subjected to empirical antibiotic therapy, while 41.17% had undergone antihistamine therapy before their admission for evaluation. None of the patients had a pre-existing medical condition, although one patient had a family (aunt) history of juvenile rheumatoid arthritis.

Median duration of fever was 16 days (range 11-50 days). The most common complaints were fever (100%), rash (94.11%), arthritis (70.58%), arthralgia (64.70%), intra-articular effusion (35.29%), hepatomegaly (47.05%), splenomegaly (41.17%), and lymphadenopathy (64.70%). Clinical findings of the patients are summarized in Table 1. No macrophage activation syndrome (MAS) developed during the follow-up of patients.

The most common laboratory findings were leukocytosis (76.47%), elevated C-reactive protein (CRP) (100%), elevated erythrocyte sedimentation rate (ESR) (100%), hyperferritinemia (100%), and positive antinuclear antibody (ANA) (35.30%). All patients had normal levels of albumin, urea, creatinine, and complement components C3 and C4. Laboratory findings of the patients are summarized in Table 2.

All patients had normal echocardiographic and ophthalmologic examinations, peripheral blood smears, bone marrow aspirations (performed in 64.70% of patients), computed tomography scans of the abdomen and thorax (obtained in 70.58% of patients), viral serology testing, urine and blood cultures, Brucella testing, and immunoglobulin M, A, and G levels (examined in 82.35% of patients). The following treatment regimens were prescribed: Pulse steroids (nine patients), ibuprofen (eight patients), methotrexate (nine patients), low-dose steroids (two patients), and IL-1 antagonists (two patients).

Discussion

Fever is a prevalent symptom in children and can be categorized as either focal or non-focal. When it comes to FUO in pediatric population, primary underlying causes

Table 1. Clinical findings of the patients with systemic juvenile idiopathic arthritis

Patient ID no.	Age (months)/ Sex	Duration of Ever	Fever	Arthritis	Rash	Hepatomegaly	Splenomegaly	Arthralgia	Joint Effusion
1	60/M	18	+	+	+	-	+	+	-
2	60/M	15	+	+	+	-	-	+	-
3	18/M	40	+	-	+	+	+	-	+
4	168/F	25	+	-	+	-	+	+	-
5	72/F	50	+	+	+	+	-	-	+
6	168/M	13	+	-	+	+	+	+	-
7	36/M	12	+	+	-	-	-	+	-
8	144/M	16	+	+	+	+	-	-	+
9	36/F	20	+	+	+	-	-	+	+
10	120/F	15	+	-	+	-	-	+	-
11	108/F	18	+	+	+	+	-	+	-
12	168/M	11	+	+	+	+	+	+	-
13	60/M	14	+	+	+	+	-	+	-
14	169/F	12	+	-	+	-	+	+	-
15	53/M	25	+	+	+	-	-	-	+
16	9/M	15	+	+	+	+	+	-	+
17	84/M	20	+	+	+	-	-	-	-

M: Male, F: Female.

Table 2. Laboratory findings of the patients with systemic juvenile idiopathic arthritis

Patient ID no.	CRP (mg/L)	Ferritin (ug/L)	Erythrocyte Sedimentation Rate (mm/h)	Leukocyte Count (mm^3)	Neutrophil count (mm^3)	Antinuclear Antibody
1	220	456	85	26100	18600	Positive
2	138	180	57	15400	11900	Negative
3	87	1492	56	18300	10000	Positive
4	105	7694	70	19600	15300	Negative
5	124	516	95	8900	3700	Positive
6	105	7180	50	17140	13470	Negative
7	46	817	29	9700	5000	Positive
8	34	310	17	8100	4400	Negative
9	52	216	34	7600	2900	Positive
10	144	1148	97	20680	16570	Negative
11	206	9980	102	11850	6280	Negative
12	321	511	50	17700	15600	Negative
13	182	480	55	14150	10910	Negative
14	76	669	71	13300	9650	Positive
15	34	1772	83	19420	13570	Negative
16	257	417	48	36630	29040	Negative
17	80	440	62	31080	26230	Negative

CRP: C-reactive protein.

typically fall into categories such as infections, connective tissue disorders, and neoplasms. One of the most common connective tissue disorders associated with FUO is sJIA (9). It stands as the most prevalent rheumatic disease affecting children. Main characteristic findings include an onset before 16 years of age, lasting longer than six weeks, and presence

of arthritis of unknown etiology. JIA is very rare in infancy and has the highest incidence rate during the preschool years. It is not a single disease entity but rather a spectrum of diseases with some shared features of distinct immunopathogenesis and clinical manifestations (10).

During the study, 212 patients were examined with FUO and 8% were diagnosed with sJIA, 20% with hematological malignancy, and 54% with infectious diseases. Our study included 17 patients with sJIA after thorough evaluations that ruled out infectious diseases (through blood culture, urine culture, and viral serology testing), malignant diseases (via peripheral blood smear and bone marrow aspiration), and other rheumatic diseases through the necessary diagnostic work-ups. In a separate study of 93 patients with FUO, 79 (84.9%) were found to have an underlying etiology. Infectious diseases were the most common cause (37.6%), followed by malignancies (17.2%), miscellaneous diseases (16.1%), and collagen vascular diseases (14.0%) (11).

Median age in our study was six years (range nine months to 14 years), with 64.70% male and 35.30% female. Comparatively, in a previous study involving 75 sJIA patients, mean age at diagnosis has been reported as 6.45 ± 4.80 years, with a slightly higher male representation at 56% and 44% female (12). One patient in our study had an aunt with juvenile rheumatoid arthritis. In another study of sJIA patients, familial connections were observed as well. One patient had an aunt with arthritis, and another had a sister with human herpesvirus-6-related infantile rheumatoid arthritis (13). A broader perspective from a study encompassing 116 patients with various subtypes of JIA indicated a positive family history rate of 11.2% (14). These familial links raise questions about the genetic factors contributing to the development of rheumatic diseases in certain families.

In our study, we found that the median duration of fever in our patients was 16 days (ranging from 11 to 50 days). Prior to their admission for evaluation, a significant portion of patients (58.80%) had received empirical antibiotic therapy as part of the initial management of their fever. Comparing these findings with another study, where the mean duration of fever was reported as 28.6 days (ranging from 10 to 90 days), we observed that fever duration in our patients was relatively shorter on average. In the same study, two different antibiotics (2.0 ± 1.6) were administered for prolonged fever before a definitive diagnosis was established, with a maximum of up to five different antibiotics used in some cases (13). Such differences in fever duration and antibiotic usage highlight the variability in clinical presentations and diagnostic journeys of patients with sJIA, thus underscoring the need for a comprehensive approach.

The most frequently shared clinical findings among our patients were fever (100%), rashes (94.11%), and arthritis (70.58%). Comparing our findings to previous ones in the literature on sJIA, we can note some similarities: The most common clinical findings at the time of diagnosis included fever (100%), arthritis (78.7%), and rashes (66.2%) (12). In another study, the most common three symptoms in sJIA patients were reported as fever (100%), rashes (63%), and arthritis (75%), followed by hepatosplenomegaly (63%), lymphadenopathy (50%), pulmonary symptoms (13%), and myalgia (25%) (13).

It should be noted that none of our patients exhibited uveitis, and all patients had normal results in their echocardiographic examinations. In contrast, a study conducted by Saurenmann et al. with a larger cohort of 1081 patients diagnosed with JIA found varying subtypes. In that study, 61% of patients had oligoarticular JIA, 22% had polyarticular JIA, and 0.7% were identified as having sJIA (15). Besides, previous research involving 50 patients with JIA reported mild mitral valve insufficiency in one patient (16).

In cases of sJIA, certain laboratory findings are expected, including leukocytosis and elevated levels of CRP, ESR, and ferritin (17). Our laboratory results corroborated these expectations, as we observed neutrophilic leukocytosis, increased ESR, elevated CRP, thrombocytosis, and hyperferritinemia among our patients. These findings align with other studies in the field. For instance, a study involving 82 patients with sJIA found that individuals with sJIA exhibited elevated ESR, CRP, and leukocyte levels, reflecting the systemic inflammatory nature of the condition (18). Interestingly, previous research conducted in our country has reported that leukocyte counts, ESR, and CRP levels are higher in sJIA when compared to other subgroups of JIA, underscoring the unique laboratory profile of the disease (19). Besides, Sarkar et al. have reported that ESR, CRP, and ferritin levels are higher in patients with sJIA in a study of 40 patients, emphasizing the significance of hyperferritinemia as a characteristic feature (20). In our study, we also found that C3 and C4 levels were within the normal range, and the rate of positive ANA tests was 64.70%. These findings offer insights into the immunological aspects of sJIA. A previous study has reported that 54% of patients had positive ANA tests, and all patients exhibited normal C3 and C4 levels, which is in line with our findings (13).

MAS is a severe and potentially life-threatening complication associated with sJIA, demanding swift evaluation and treatment to ensure the best possible outcomes (6). In a significant portion of cases, approximately 10% of children with sJIA, MAS presents as an overt complication (21). In our study, it is likely that the early diagnosis and treatment of sJIA prevented MAS by controlling the underlying inflammation and preventing the overactivation of macrophages.

The primary approach to treating sJIA typically involves corticosteroids, administered in various doses and routes (oral,

intravenous, and intraarticular), often in combination with disease-modifying anti-rheumatic drugs like methotrexate, sulfasalazine, and leflunomide. These initial treatments are aimed at controlling inflammation and managing the symptoms of sJIA. In cases where sJIA proves to be refractory to these first-line therapies, the use of biological agents becomes a valuable addition to the treatment regimen (5). In one study, for instance, biological agents were employed in the treatment of 58.6% of patients diagnosed with sJIA, and similarly in a study from our country, which involved 116 patients with various subtypes of JIA, about 46.6% of patients with sJIA received treatment involving methotrexate (14,19). In our study, therapy regimens were tailored to the individual clinical status of patients, which ensured that each patient received a treatment plan suited to their unique medical condition and needs.

sJIA should be considered in the differential diagnosis of FUO, especially in children. Early diagnosis and treatment can significantly improve outcomes. Typical clinical manifestations include prolonged fever, rashes, elevated acute phase reactants, and hyperferritinemia. However, lack of specific biomarkers, diverse clinical presentations, and the overlap of symptoms with various other conditions render the diagnosis of sJIA a challenging task. Vigilance and a comprehensive approach are thus crucial in identifying and managing this complex rheumatic disease.

Ethics Committe Approval: This study was obtained from Necmettin Erbakan University Meram Faculty of Medicine non-Pharmaceutical and Medical Device Research Ethics Committee (Decision no: 2020/2843, Date: 02.10.2020).

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