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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

ÇOCUKLUK ÇAĞINDA SAPTANAN ARTRİT VAKALARININ RETROSPEKTİF OLARAK İNCELENMESİ

RETROSPECTIVE INVESTIGATION OF ARTHRITIS CASES DETECTED IN CHILDHOOD

Hatice BÜYÜKOFLAZ[1], Muhammed Yaşar KILINÇ[2]

[1]Konya Şehir Hastanesi, Çocuk Sağlığı ve Hastalıkları Bölümü
[2]Afyonkarahisar Devlet Hastanesi, Neonatoloji Bölümü

ÖZET

AMAÇ: 01.01.2012 ile 31.12.2014 arasında Karaman Eğitim Araştırma Hastanesi Çocuk Sağlığı ve Hastalıkları servisinde artrit tanısı alan hastaların dosyalarının retrospektif olarak incelendiği bu çalışmada hastaların anamnez, fizik muayene ve laboratuvar tetkiklerinin incelenerek artrit etyolojilerinin değerlendirilmesi amaçlanmıştır.

GEREÇ VE YÖNTEM: Toplam 101 hastanın bilgileri retrospektif olarak dosya taraması yöntemi ile incelendi. Tam kan sayımı (CBC), eritrosit sedimantasyon hızı (ESR), C-reaktif protein (CRP), kan kültürü, antinükleer antikor (ANA), antistreptolisin-O (ASO), romatoid faktör (RF), ailevi akdeniz ateşi (FMF) gen mutasyonu ve hepatit virüsleri, insan immün yetmezlik virüsü, Salmonella, *Mycoplasma pneumoniae (M. pnömoni)*, su çiçeği, Epstein-Barr virüsü, Parvovirüs, Kızamıkçık, Yersinia, Kampilobakter, Brusella gibi serolojik degerlendirme sonuçları ve/veya kültür gibi mikrobiyolojik degerlendirme sonuçları incelendi.

BULGULAR: Olguların ilk başvuru yaşları 1-17 yıl (ortalama 9.74±3.9) arasındaydı. Çalışmamızda 101 hastanın E/K oranı 1.4 idi. Olgular tanılara göre incelendiğinde %32'si geçici artrit, %15'i juvenil idiopatik artrit, %12'si akut romatizmal ateş, %10'u Ig A vasküliti, %8'i reaktif artrit, %6'sı Bruselloz artriti, %6'sı poststreptekoksik reaktif artrit, %3'ü ailevi Akdeniz ateşi, %2'si Kawasaki hastalığı artriti, %2'si septik artrit, %1'i viral artrit, %3'ü ürtikeryal vaskülit olarak saptandı. Çalışmamızda hastaların %45.5'inde yakın zamanda geçirilen üst solunum yolu enfeksiyonu hikayesi mevcuttu. Hastaların %42.4'ünde lökositoz, %45.5'inde CRP yüksekliği, %54.8'inde ESR yüksekliği bulunuyordu. Hastaların %76.3'ünde akut, %4.9'inde subakut eklem tutulumu saptanırken, %18.8'unda kronik eklem tutulumu gözlenmiştir. Olguların %65.3'ünde diz tutulumu saptanırken, 2. sıklıkta tutulan eklem ayak bileği idi. Artrit tanısı ile takip edilen hastalar en sık diz ağrısı (%65.3) ve ayak bileği ağrısı (% 31.6) ile başvurmuştur. Hastalarda en sık ateş (%36.6), döküntü (%15.8), kas ağrısı (%6.9) ek şikayeti vardı. Romatizmal ateş, reaktif artrit, juvenil idiopatik artrit, poststreptekoksik reaktif artritte en sık diz tutulumu mevcutken, Ig A vasküliti ve ailevi Akdeniz ateşi'nde en sık ayak bileği tutulumu gözlenmiştir.

SONUÇ: Artrit tanısı alan hastada yakınmanın süresi, gezici ve tekrarlayıcı özelliği, hangi eklemin tutulduğu, ek yakınma, aile öyküsü, muayene bulguları, akut faz reaktanlarının yüksekliği ve diğer ek laboratuvar tetkikleri ayırıcı tanıda yardımcı olabilir. Tanıda öykü, fizik muayene bulguları çok önemli olmakla birlikte, laboratuvar bulguları da değerlidir.

ANAHTAR KELİMELER: Artrit, Juvenil, Bruselloz, Ailevi Akdeniz Ateşi, IgA.

ABSTRACT

OBJECTIVE: In this retrospective study, we aimed to evaluate the etiology of arthritis by examining the anamnesis, physical examination and laboratory tests of the patients between 01.01.2012 and 31.12.2014 in Karaman Training and Research Hospital Pediatrics Department.

MATERIAL AND METHODS: The data of 101 patients were retrospectively analyzed. We recorded the results of laboratory investigations, including complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood culture, antinuclear antibody (ANA), antistreptolysin-O (ASO), rheumatoid factor (RF), Familial Mediterranean Fever (FMF) gene mutation, and serological tests including hepatitis viruses, human immunodeficiency virus, Salmonella, *Mycoplasma pneumoniae (M. pneumonia)*, Chickenpox, Epstein-Barr virus, parvovirus, Rubella, Yersinia,Campylobacter, Brucella, and microbiological tests such as culture were analyzed.

RESULTS: The age at initial presentation ranged from 1 to 17 years (mean: 9.74±3.9). In our study, the M/F ratio of 101 patients was 1.4. Diagnostic analysis revealed that 32% of the patients had transient arthritis, 15% had juvenile idiopathic arthritis (JIA), 12% had acute rheumatic fever (ARF), 10% had IgA vasculitis, 8% had reactive arthritis (RA), 6% had Brucella arthritis, 6% had poststreptococcal reactive arthritis (PSRA), 3% had Familial Mediterranean Fever (FMF), 3% had urticarial vasculitis, 2% had arthritis associated with Kawasaki disease, 2% had septic arthritis, and 1% had viral arthritis. In our study, 45.5% of the patients had a recent upper respiratory tract infection history. Leukocytosis was present in 42.4% of patients, elevated CRP in 45.5%, and elevated ESR in 54.8%. Joint involvement was acute (<2 weeks) in 76.3% of patients, subacute (2-6 weeks) in 4.9%, and chronic (>6 weeks) in 18.8%. The most common complaints were knee pain (57.3%) and ankle pain (31.6%). Additional symptoms included fever (36.6%), rash (15.8%), and muscle pain (6.9%). In patients with ARF, RA, and Juvenile Idiopathic Arthritis (JIA), the knee was the most commonly affected joint, while the ankle was most frequently involved in patients with IgA vasculitis and FMF.

CONCLUSIONS: In patients diagnosed with arthritis, the duration of symptoms, migratory or persistent nature of arthritis, the number of affected joints, associated symptoms, family history, physical examination findings, elevated acute-phase reactants, and additional laboratory tests are key factors may be helpful in the differential diagnosis. Although history and physical examination findings are very important in the diagnosis, laboratory findings are also valuable.

KEYWORDS: Arthritis, Juvenile, Brucellosis, Familial Mediterranean Fever, IgA.

Geliş Tarihi / Received: 02.05.2023
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Yazışma Adresi / Correspondence: Uzm. Dr. Muhammed Yaşar KILINÇ
Afyonkarahisar Devlet Hastanesi, Neonatoloji Bölümü
E-mail: drmuhammed007@gmail.com
Orcid No (Sırasıyla): 0000-0001-8057-2815, 0000-0001-6304-6346
Etik Kurul / Ethical Committee: Karaman Üniversitesi Tıp Fakültesi Etik Kurulu (2015/80).

INTRODUCTION

Arthritis is simply defined as inflammation of a joint, which may affect one or more joints and is often accompanied by swelling, redness, tenderness, warmth, and pain during movement (1). Extremity complaints are common in children, accounting for up to 10% of non–well-child visits to pediatricians (2). In contrast, rheumatologic conditions are rare, affecting fewer than 200,000 children in the United States (3). Therefore, clinicians who care for children must have an efficient and effective approach to distinguish arthritis, lupus, and other autoimmune conditions from injuries, infections, tumors, and non-inflammatory causes of extremity complaints (4). Joint pain and swelling are common symptoms of many musculoskeletal and rheumatologic diseases, as well as a wide range of non-rheumatic conditions (5). The differential diagnosis for childhood joint pain and swelling is extensive and includes both benign and serious conditions (6). Assessment of a child with joint pain and/or swelling should be conducted with urgency, especially for conditions with potentially serious consequences (7 - 9). The present study aimed to determine the predisposing factors and etiology of arthritis in children through history, physical examination, and laboratory tests.

MATERIALS AND METHODS

In this study, the files of patients hospitalized with a diagnosis of arthritis (defined as swelling, redness, pain, increased warmth, and loss of function in at least two joints) at KaramanT-raining and Research Hospital Pediatric Service between January 2012 and December 2014 were retrospectively analyzed and evaluated. We documented patients' age, sex, detailed medical history, physical examination findings, and results of laboratory investigations, including complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood culture, Antinuclear Antibody (ANA), Antistreptolysin-O (ASO), Rheumatoid Factor (RF), FMF gene mutation, and serological tests for hepatitis viruses, Human Immunodeficiency Virus, and Salmonella. Results from additional laboratory studies and serological/microbiological evaluations, including cultures for *Mycoplasma pneumoniae*, Varicella, Epstein-Barr virus, Parvovirus, Rubella, Yersinia, Campylobacter, and Brucella, were also recorded. Electrocardiography (ECG) and echocardiography (ECHO) results were examined, and radiological imaging including X-ray, ultrasonography, and MRI findings was utilized. Diagnoses were categorized according to the current guidelines published by the American College of Rheumatology, American Rheumatism Association, American Academy of Pediatrics, and American Heart Association.

Ethical Committee

The Institutional Review Board approved the study, and informed consent was obtained from the patient's parents. Additionally, the study received ethical approval from the ethics committee of Karaman University Faculty of Medicine, with the ethics committee number 2015/80.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0. Parametric results were reported as mean ± standard deviation, while non-parametric results were expressed as percentages. T-tests (Student's T-test) were used for parametric data, and chi-square tests were employed for non-parametric data in one-to-one comparisons. Pearson correlation tests were used for correlation analysis of the case data. Multiple linear regression analyses were conducted for variables showing significant correlation ($r>0.500$). The statistical significance level was set at $p<0.05$ for all tests.

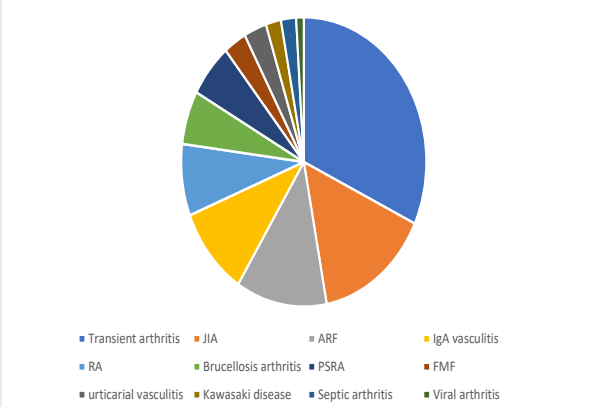
RESULTS

The diagnoses of patients were classified as follows: transient arthritis (32%), JIA (15%), ARF (12%), IgA vasculitis (10%), RA (8%), Brucellosis arthritis (6%), PSRA (6%), FMF (3%), urticarial vasculitis (3%), Kawasaki disease arthritis (2%), septic arthritis (2%), and viral arthritis (1%). The distribution of arthritis cases according to diagnoses is shown in **Graph 1**.

Of the patients, 41.6% [n=42] were female, and 58.4% [n=59] were male. The male-to-female ratio was 1.4. There was no significant gender difference between the diagnostic groups [p=0.274]. The average age at first presentation of the cases was 9.74 ± 3.9 years (range 1-17 years).

Family history was present in 66.7% of FMF patients, 33.3% of brucellosis patients, 13.3% of JIA patients, 8.3% of ARF patients, and 2.5% of RA patients. There was no significant difference in family history between the diagnostic groups.

The patients most frequently presented with knee pain (57.3%) and ankle pain (31.6%). As additional complaints, the patients most frequently presented with fever (36.6%), rash (15.8%), and muscle pain (6.9%). The most common presenting findings are given in **Table 1**.



ARF: Acute rheumatic fever, JIA: Juvenil idiopatik arthritis, PSRA: Poststreptoccal reactive arthritis,

RA: Reactive arthritis, FMF: Familial Mediterranean Fever

Graph 1: Distribution of Arthritis Cases According to Diagnoses

Table 1: The most common presenting findings

	n	%
Fever	37	36,6
Rash	16	15,8
Abdominal pain	7	6,9
Muscle pain	9	8,9
Weakness	8	7,9
Other	5	4,9

The most common physical examination findings were fever in FMF, brucellosis, septic arthritis patients, rash in urticarial arthritis patients, lymphadenopathy, and murmur in Kawasaki patients, murmur in ARF patients, and abdominal tenderness in IgA vasculitis and FMF patients.

Asymmetric joint involvement was seen especially in ARF (100%) and Kawasaki disease (100%), while symmetrical joint involvement was most common in IgA vasculitis (80%). When the distribution of patients according to joint involvement time was examined, 76.3% acute, 4.9% subacute, and 18.8% chronic joint involvement was observed. While acute joint involvement was observed in most cases, chronic joint involvement was found in JIA (53.3%) and urticarial arthritis (66.6%).

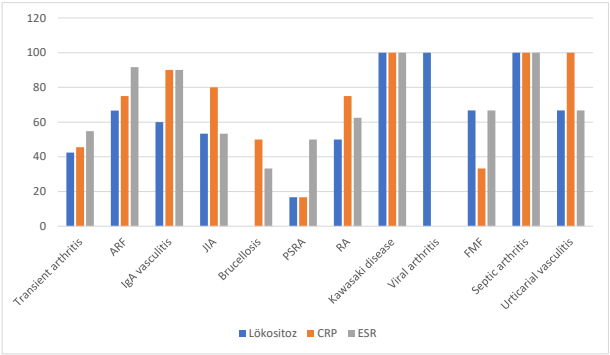
When joint involvement was examined according to the diagnoses, the most common knee involvement was observed in ARF, RA, JIA, and PSRA, while the most common ankle involvement was observed in IgA vasculitis and FMF **Table 2.**

Table 2: Joint involvement

Diagnosis	Knee	Ankle	Hip	Elbow
Transient arthritis	12 (36%)	6 (18%)	16 (48,6%)	1 (3%)
ARF	7 (58,3%)	3 (25%)	2 (16,7%)	1 (8,3%)
IgA vasculitis	2 (20%)	8 (80%)	0	0
JIA	8 (53,3%)	5 (33,3%)	1 (6,7%)	1 (6,7%)
Brucellosis	3 (50%)	2 (33,3%)	5 (83,3%)	0
PSRA	4 (66,7%)	1 (16,7%)	0	0
RA	6 (60%)	1 (10%)	2 (20%)	0
Kawasaki disease	1 (50%)	1 (50%)	0	0
Viral arthritis	1 (100%)	0	0	0
FMF	1 (33,3%)	2 (66,7%)	0	0
Septic arthritis	1 (50%)	0	1 (50%)	0
Urticarial vasculitis	1 (25%)	1 (25%)	1 (25%)	1 (25%)

ARF: Acute rheumatic fever, JIA: Juvenil idiopatik arthritis, PSRA: Poststreptoccal reactive arthritis, RA: Reactive arthritis, FMF: Familial Mediterranean Fever

Leukocytosis was detected at a rate of 67% in ARF, FMF, and urticarial arthritis, 53% in JIA, and 100% in Kawasaki disease, viral arthritis, and septic arthritis. CRP and ESR elevation were 92% in ARF, 53% in JIA, 62% in RA, 100% in Kawasaki disease and septic arthritis, and 67% in FMF and urticarial arthritis. The highest mean leukocyte count was detected in septic arthritis and Kawasaki disease, and the highest mean CRP and ESR were found in Kawasaki disease. If complaints of fever and rash are accompanied by high levels of acute-phase reactants, more serious pathologies should be considered as the cause of arthritis. Leukocytosis, CRP, and ESR elevation in the percentage of the cases according to the diagnoses are shown in **Graph 2**.



ARF: Acute rheumatic fever, JIA: Juvenil idiopatik arthritis, PSRA: Poststreptoccal reactive arthritis,

RA: Reactive arthritis, FMF: Familial Mediterranean Fever

Graph 2: Leukocytosis, CRP and ESR elevation in percentage of the cases

45.5% of transient arthritis patients had a history of recent upper respiratory tract infection, and 4% had a history of trauma. Recovery was observed in 79% of the patients within 2 weeks.

JIA was of the polyarticular type in 5 patients (33.3%), oligoarticular type in 6 patients (40%), and systemic type in 4 patients (26.7%). In our study, positive ANA rates in JIA were found as 66% in oligoarticular type, 100% in polyarticular RF (+) type, and 50% in polyarticular RF (-) type. Uveitis was not observed in any of the patients.

75% of ARF patients had a history of recent upper respiratory tract infection. Murmur was detected in 58.3% of the cases. 66.7% of patients had ASO elevation. PR length was present in 8 cases (67%). Mitral insufficiency and 16.7% aortic insufficiency were found in 75% of the patients. Four of the 6 patients diagnosed with PSRA had a history of previous upper respiratory tract infection. 66.7% of patients had ASO elevation.

Patients with RA had a recent history of acute gastroenteritis, 5 of them had salmonella, and 3 had Shigella in the stool culture of 8 patients. Of the 6 patients diagnosed with Brucellosis, 2 had unpasteurized cheese, and 2 had a family history. 2 of the patients had leukopenia. M694V heterozygous mutation in the MEFV gene was found in 2, and M694V homozygous mutation in the MEFV gene in 1 of the 3 patients diagnosed with FMF.

DISCUSSION

Joint complaints in a child can be the first sign of many different diseases. Joint pain and arthritis can have numerous causes, which can be difficult to distinguish. Unfortunately, there is no standard diagnostic approach to investigate arthritis in children. The prevalence of any musculoskeletal problem is significantly higher in males than in females worldwide (9). However, in our study, we found no difference in diagnosis distribution between genders.

Differences have been reported in the rates of arthritis causes in the literature. Mostly, arthritis is reported as the most common cause of toxic synovitis, although in some studies, JIA and septic arthritis have also been reported as the most common causes of arthritis (9 - 12). In our study, the causes of arthritis were transient arthritis, JIA, ARF, IgA vasculitis, RA, brucellosis arthritis, PSRA, FMF, urticarial vasculitis, Kawasaki disease arthritis, septic arthritis, and viral arthritis in descending frequency.

The first admission age of our cases with arthritis was between 1-17 years (mean 9.7 ±3.9). When the age distribution was examined, no significant difference was found. In our study, transient arthritis was in the first place with a rate of 32%. Consistent with the literature, the mean age of patients with transient arthritis was 9.7 (13).

In patients with transient arthritis, hip joint involvement was more frequent, with a rate of 48.6%, which was consistent with other studies (9, 14). Kastrissianakis et al. (15) reported that patients had transient pre-arthritic upper respiratory tract infection and gastroenteritis symptoms. In our study, 45.5% of the patients had a recent history of upper respiratory tract infection. Again, consistent with the literature, improvement was observed in 79% of the patients within 2 weeks (16).

In our study, JIA was the second most common cause of arthritis. According to the literature, oligoarticular JIA, a subgroup of JIA, was found at a higher rate in our study (17). The rates of ANA (+) in JIA subtypes were consistent with the literature (18).

The third leading cause of arthritis was ARF with 12%. While these two studies were consistent with the rates of 15% and 18% stated for ARF (11,19), they were not compatible with the rates of 9%, 38.6%, and 41% found in three more recent studies conducted in our country (20 - 22). Although it is thought that the difference between studies is due to regional variation, it shows that ARF is still a very important health problem in developing countries such as ours. In a study, PR prolongation was found with a frequency of 17.3% in patients diagnosed with ARF (23). In our study, PR prolongation was found in 66.7% of patients diagnosed with ARF. Although, remarkably, the PR prolongation is higher than in the literature, it was not considered correct to generalize due to the low number of cases. ASO elevation was present in 66.7% of ARF patients. Consistent with our study, ASO elevation was found to be significantly higher in two other studies (22, 24).

In our study, IgA vasculitis was the fourth most common etiology of arthritis (10%). In a thesis

study, the frequency of IgA vasculitis was found to be 5.5% in patients with arthritis (24). Our IgA vasculitis patients often had ankle involvement, which was consistent with other studies (25, 26). While leukocytosis was detected in 60% of our patients with IgA vasculitis, it was found in 78% in another retrospective study (27).

RA was detected in 8% of our patients. In our study, large joint involvement was more common, which was consistent with the literature (28). Evidence of infection was found in all patients with RA; Salmonella Typhimurium was grown in the stool cultures of five patients, and *Shigella flexneri* was grown in the stool cultures of three patients. In the study of Riise et al. (9), evidence of infection was found in 27% of the patients, and no infectious agent was found in the remaining patients with RA.

Brucellosis still maintains its importance in our country and other developing countries. In our study, the rate of brucellosis in the etiology of arthritis was found to be 6%. Various studies in children have shown that the rate of arthritis in patients with brucellosis differs. This rate ranged between 5.7-85% (29 - 31). The most common involvement was in the sacroiliac joint. Brucellosis can progress with many different signs and symptoms. Therefore, this disease should be considered, especially in regions where Brucella is endemic.

In our study, unlike the studies on the etiology of arthritis, FMF arthritis was detected much more frequently with a rate of 3%. Since FMF disease is common in our country, FMF should be considered in the differential diagnosis of patients with recurrent fever, abdominal pain, and joint complaints.

Septic arthritis, which was found with a frequency of 3% in our study, was characterized by single joint involvement, by the literature. The most common large joint involvement was hip, knee, and shoulder (32, 33). In various studies, it has been reported that 22-59% of patients with septic arthritis have growth in blood culture (2). *S. aureus* was grown in the blood culture of our patients with septic arthritis.

In our study, the most frequently involved joints in all cases were the knee (65.3%), ankle (31.6%), and hip (15.6%), similar to other studies (9,21). Except for cases with IgA vasculitis, our patients frequently presented with asymmetric joint involvement, as found in other studies (19).

Many infectious, rheumatic, hematological, or orthopedic diseases can cause arthritis in childhood. As a result, in single joint involvement with fever, infections should be considered first, and especially the possibility of septic arthritis and osteomyelitis should be evaluated. In our country, brucellosis and salmonellosis should be considered in the differential diagnosis of hip joint and waist pain accompanied by fever. All cases of acute migratory polyarthritis, especially in school-age children, should be evaluated for acute rheumatic fever until proven otherwise in our country.

In our study, we aimed to highlight various differential diagnoses and features in the etiology of arthritis. The importance of differential diagnosis remains significant due to the absence of a universally accepted diagnostic algorithm and the limitations of definitive diagnosis through laboratory and imaging studies. Considering regional variations in differential diagnosis, detailed anamnesis, and physical examination retain their significance. It's imperative to inquire about family history. In childhood arthritis accompanied by fever and rash, elevated levels of acute phase reactants should raise suspicion for serious causes of arthritis. Developing an algorithm for approaching arthritis based on studies conducted on childhood arthritis in our country is necessary.

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