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Clinical and Laboratory Characteristics of Juvenile Idiopathic Arthritis in Northeast Iran

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Abstract

Background: Juvenile Idiopathic Arthritis (JIA) is a chronic rheumatic disorder commonly affecting children younger than 16. The incidence and prevalence of JIA can vary greatly depending on ethnicity, genetic background, and socioeconomic status within different populations. Epidemiological studies play an essential role in planning successful treatment for chronic diseases like JIA and providing appropriate care measures in specific geographic regions.

Methods: In this cross-sectional study, 149 children were referred to the pediatric rheumatology department of Akbar Hospital in Mashhad from 2016 to 2019. Data was collected from all children within the first six months of disease onset, including the number of affected joints, demographic characteristics, systemic symptoms, extra-articular manifestations, and medication regimens.

Results: The most prevalent subtype of JIA is Oligoarticular, followed by Systemic JIA at 25.5%. Among children with enthesitis-related arthritis, more girls than boys were affected. Additionally, the most frequently affected joints in children were those of the lower limb. 5.4% of the total, had involvement of lumbosacral and sacroiliac joints. Serositis was observed in 2% of the patients. Uveitis was detected in 4 out of 154 patients (2.6%); 3 of these cases were chronic anterior uveitis, while one was acute anterior uveitis. 3 children (2%) were reported to have Macrophage Activation Syndrome (MAS).

Conclusion: Diagnosing juvenile idiopathic arthritis and other rheumatic diseases in children can often be delayed due to physicians' lacking adequate clinical knowledge. To properly manage this chronic childhood illness, it is crucial to identify its symptoms and clinical course. This study represents the most comprehensive research conducted on children with JIA in the Northeast of Iran.

Key Words: Chronic Arthritis, Oligoarthritis, Uveitis.

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1- INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is a chronic rheumatic disease that commonly affects children under the age of 16. In 1995, the International League of Associations for Rheumatology (ILAR) introduced a set of classification criteria for JIA. This criterion is based on disease presentation in the first six months of the disorder. According to the ILAR criteria of JIA, the disease has seven subtypes. JIA is classified into subtypes with variable manifestations and clinical courses: Oligoarticular JIA, Rheumatoid Factor (RF) negative polyarticular JIA, RF positive polyarticular JIA, Systemic JIA (SJIA), enteritis-related arthritis, psoriatic arthritis, and undifferentiated form. The oligoarticular is the most common subtype of JIA and usually has a good course and less joint destruction than other subtypes (1, 2). The etiology and pathogenesis of JIA are unclear. Genetic and environmental factors influence the occurrence of JIA. In most studies, oligoarticular JIA is the most common subtype. In these patients, the Management of extra-articular manifestations such as asymptomatic uveitis is of great importance. The prevalence of RF-positive Polyarticular JIA is lower during childhood, this subtype occurs more in adolescence. RF-negative Polyarticular JIA is usually seen at a young age, and due to the chronic course of the disease, manifestations such as micrognathia are more common in this form (3, 4).

JIA's worldwide incidence and prevalence vary between populations of different ethnicities, genetics, and socioeconomic statuses. Estimates of the global incidence of JIA are unknown. The majority in American and European studies varies from 4 per 100,000 to 400 cases per 100,000 population (2, 5). In some studies, such as those conducted in Japan, the prevalence of the disease has been lower (3). Epidemiological studies of chronic diseases such as JIA in specific geographic regions have an essential role in planning for more successful treatment methods and providing appropriate care measures.

This study evaluated JIA subtypes' clinical and laboratory characteristics in Northeast Iran. The results of our study and similar studies, increase knowledge about the prevalence and clinical manifestations of JIA in Iranian children and play a critical role in treating and managing this disorder.

2- MATERIALS AND METHODS

2-1. Design and Participants

In this cross-sectional study, 149 children were included, with 82 females and 67 males. They were referred to the pediatric rheumatology department of Akbar Hospital in Mashhad from 2016 to 2019. A pediatric rheumatologist examined all patients and the diagnosis of JIA was based on the ILAR and ACR (American College of Rheumatology) classification criteria. The children who participated in our study ranged in age from 1 month to 16 years old.

2-2. Procedure

JIA is diagnosed when a patient experiences chronic arthritis for more than six weeks without any signs of another underlying systemic disease that could explain the onset of arthritis. Before making a diagnosis, we investigated to identify any possible infectious sources. A serology test was performed to rule out brucellosis. Additionally, a PPD test and chest X-ray were conducted to exclude tuberculosis. A bone marrow aspiration is conducted in patients with Suspected Malignancy to rule out any abnormalities. A checklist was used to collect and record data from patients' files. This data included the number of joints affected within the first six months of disease onset, demographic characteristics, systemic symptoms such as fever or rash, extra-articular manifestations, and medication

regimens. There were frequent follow-up visits by pediatric rheumatologists, including physical examination, laboratory tests, and imaging. The hospital information system (HIS) was used to document laboratory investigations. All patients underwent an ophthalmological examination to check for the presence of uveitis. Patients with incomplete file information were excluded from the study. The analysis of the data was performed using SPSS software version 23. A p-value > 0.05 was considered statistically significant. To compare the data sets, we utilized T-test, chi-square test, and Fisher's exact test. The ethics committee of Mashhad University of Medical Sciences has approved this study (IR.MUMS.fm.REC.1396.192).

2-3. Data analysis

All statistical analyses were performed using SPSS version 23, Qualitative variables were shown as numbers and percentages. Independent samples T test or Mann Whitney U test were used to compare the numerical values of patients with JIA. The chi-square test was used to compare nominal or ordinal data. A p-value less than 0.05 was statistically significant.

3- RESULTS

Out of 149 patients studied, 82 (55.1%) were girls, and 67 (44.9%) were boys. Oligoarticular is the most common subtype of JIA, and 76 (51%) patients had involvement of ≤ 4 joints. Systemic JIA was our patients' second most common subtype (25.5%). 31(20.8%) patients had polyarticular arthritis, and 4 (2.7%) had Enthesitis-Related Arthritis (ERA). In our study, there were no significant gender differences in the variable subtypes of JIA (P=0.30) (**Table 1**).

Table-1: Characteristics of Children with Subtypes of JIA

Subtypes of JIA	Number (%)	Gender Number (%) (Male/Female)	Fever at first presentation Number (%)	Uveitis Number (%)	Joint Deformity Number (%)	Serositis Number (%)	Macrophage Activation Syndrome Number (%)
Oligoarticular	76(51)	38/38(56.7/46.3)	8(10.5)	2(2.6)	5(6.7)	-	-
Polyarticular	31(20.8)	10/21(14.9/25.6)	3(9.7)	-	2(6.5)	-	-
Systemic	38(25.5)	18/20(26.9/24.4)	36(94.7)	1(2.6)	-	3(2)	3(2)
ERA	4(2.7)	1/3(1.5/3.7)	2(50)	1(25)	-		-
psoriatic	-	-	-	-	-		-
Undifferentiated	-	-	-	-	-		-

We evaluated the frequency of initial disease signs and symptoms among the patients participating in the study (**Fig. 1**). During the initial presentation, we also analyzed the frequency of affected joints (**Fig. 2**). Out of the total patients, 32 (21.4%) reported experiencing a minor trauma before the onset of their symptoms. From among the patients diagnosed with the disease, 69 (46.3%) had previously taken oral or intravenous antibiotics, and 40 (26.8%) had a history of using NSAIDs. The parents of 35 cases (26.1%) were in a consanguineous relationship. 19 patients (12.8%) had a family history of the disease. The demographic characteristics are shown in **Table 2**.

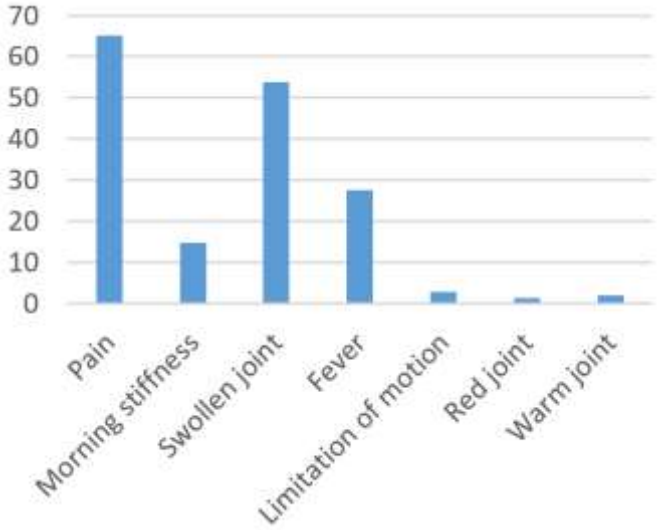

Fig 1: The frequencies (%) of initial disease signs and symptoms in patients

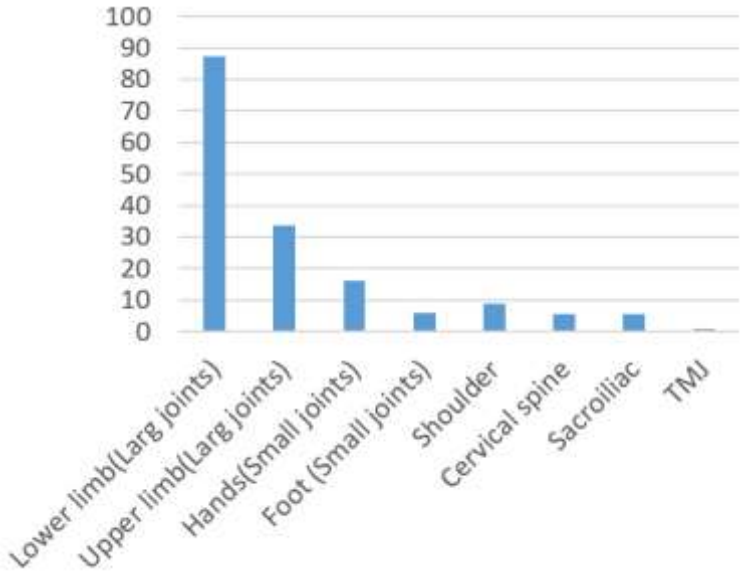

Fig 2: The frequencies (%) of affected joints at initial presentation in patients

Table-2: Demographic data and other characteristics of the patients

characteristics	All subtypes of JIA
Age of onset (years) (mean ± SD)	6.85± 3.9
The intervals between first manifestation and diagnosis (days) (mean ± SD)	120± 218.19
Hospital admission time (days)	4.79± 2.6
Sex	
Female	19(12.8%)
Male	35(26.1%)
Positive family history	88(55.1%)
Parents blood relatives	67(44.9%)

The frequency of systemic symptoms and organ involvement in patients with SJIA was examined (**Fig. 3**).

The patients commonly experienced fever as their primary symptom, followed by the development of a rash. Macrophage Activation Syndrome (MAS) occurred in 3 patients with SJIA (**Table 1**). 7 (4.7%) patients had joint flexion contracture and deformity during the disease course. Uveitis was reported in only 4 (2.6%) patients. Laboratory test results are shown in **Table 3**.

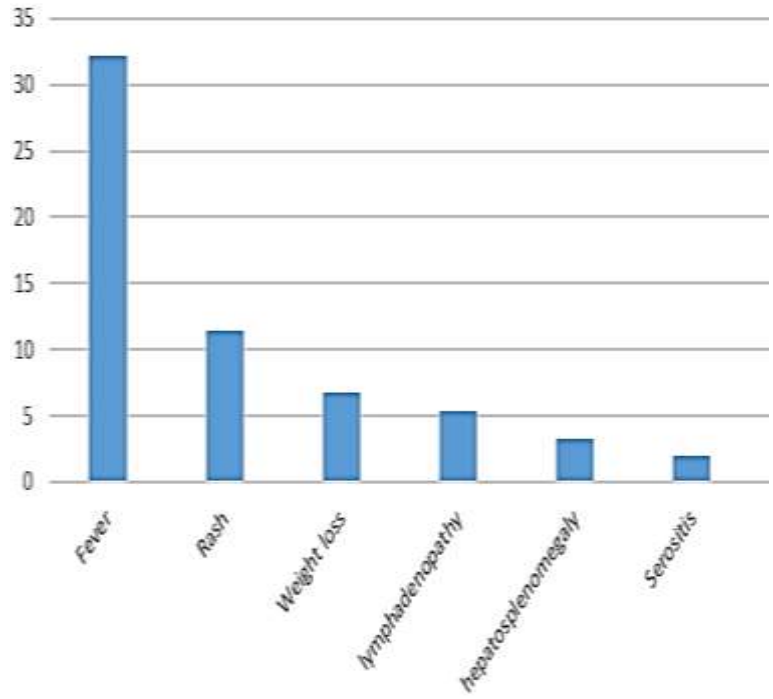

Fig. 3: The frequencies (%) of clinical symptoms in patients with SJIA

Table-3: Laboratory tests results

Laboratory tests	All subtypes of JIA
White blood cell/Ml (mean ± SD)	11612.33± 3.6
Platelets/MCL (mean ± SD)	287421.92± 6.8
erythrocyte sedimentation rate (ESR) (mean ± SD)	30.15± 5.7
C-reactive protein (CRP) mg/dl (mean ± SD)	28.18± 7.2
ANA Positive	12(8%)
RF Positive	13(8.7%)
Anti-CCP Positive	8(5.4%)
HLA B27 Positive	2(1.3%)

ANA: Antinuclear antibody RF: rheumatoid factor, Anti-CCP: Anti-cyclic citrullinated Peptides, HLA-B27: Human Leukocyte Antigen-B27

12 out of 149 patients had positive ANA results, 13 had positive RF (Rheumatoid Factor) test, and 8 had positive anti-CCP. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) were the first line of treatment for all patients. The frequency of drug use in patients is shown in **Fig. 4**.

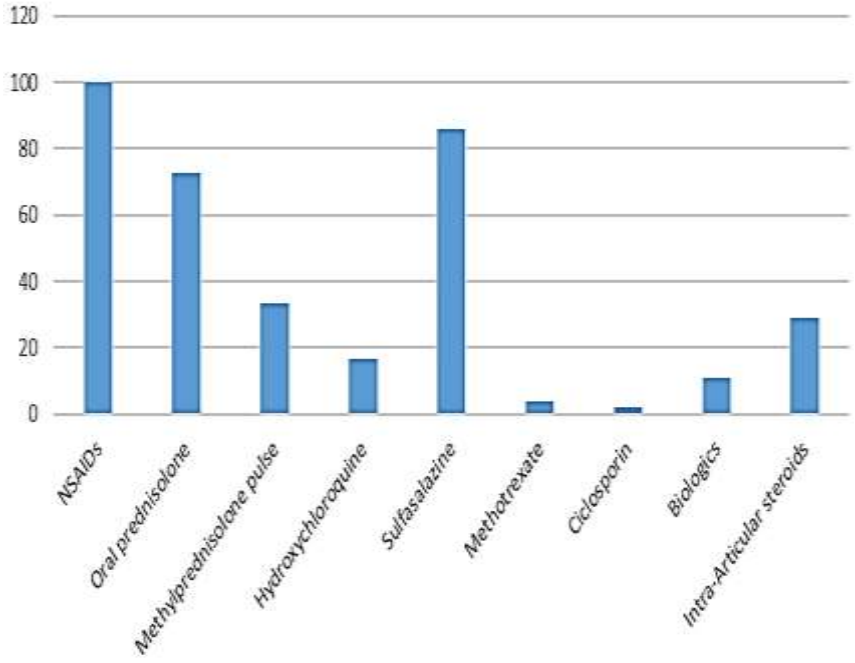

Fig. 4: The frequencies (%) of drugs used in patients

4- DISCUSSION

JIA is the most common of childhood rheumatic diseases. JIA usually affects children under age 16. The condition often had a subtle and gradual presentation. There has not been a thorough epidemiological investigation conducted on Juvenile Idiopathic Arthritis (JIA) in northeastern Iran. The study was conducted at the Department of Pediatric Rheumatology in Akbar Hospital in the northeast region of Iran.

Our study revealed that the most common subtype of JIA was oligoarticular, which is consistent with the findings of previous studies. The second most common subtype was systemic JIA, similar to research conducted in the Middle East region (1, 3, 4). In North America and Europe, the second most common subtype was RF-negative polyarticular JIA. These studies revealed that oligoarticular JIA is more prevalent among girls. However, in some research carried out in Asia and Africa, oligoarthritis has been found to be more common among boys (2, 5). Our study discovered that the female-to-male ratio is approximately 1.2:1.

The incidence rate for patients with ERA subtype was higher in boys than in girls. In this study, it was observed that there were a higher number of girls than boys with ERA. The joints of the lower limbs were the most commonly affected joints in children. Our study revealed that the knee joint was the most frequently impacted. Cervical spine involvement can be asymptomatic; and Involvement of the cervical spine is associated with significant disability and risk of Atlantoaxial Instability (4-6). In this study, Cervical spine joints were affected in 8 (5.4%) patients. This result highlights the importance of early diagnosis of cervical spine involvement in asymptomatic patients.

Only 8 (5.4%) patients had involvement of the lumbosacral and sacroiliac joints. Even in the ERA subtype, the involvement of these joints may occur later in the disease course.

Systemic symptoms such as fever were reported in 36 (94.7%) patients with SJIA and 2(50%) patients with ERA. In other studies, the high occurrence of fever in the ERA subtype was not reported. Patients with ERA may show increased acute phase reactants, such as ESR and CRP, similar to those with SJIA (2, 7).

3 (2%) children observed had serositis, specifically pericarditis. It was noted that all 3 of these patients had Systemic Juvenile Idiopathic Arthritis (SJIA). Pericarditis was the most prevalent cardiac manifestation observed in children, but it was only found in patients with SJIA. This subtype is known to have a higher occurrence of serositis than others (8).

The average duration of the first visit until the initial diagnosis of JIA was 120±21.19 days. It was longer than some studies in other countries. Therefore, the Awareness of this chronic disorder among physicians can improve the early diagnosis of JIA in children. During the diagnosis, ultrasonography reported synovial hyperplasia in 12 patients (27.2%); this finding also indicates a long interval between the onset of symptoms and the diagnosis (1, 2, 6).

Macrophage Activation Syndrome (MAS) was reported in 3 (2%) children, one patient developed MAS at the first visit. According to previous studies, MAS is a potentially life-threatening complication usually occurring during active disease. MAS may occur at the time of initial diagnosis (9).

Although some family studies suggest that genetics may contribute to the development of JIA, it is uncommon for JIA to affect multiple family members. However, among family members with arthritis, the onset type and the likelihood of developing uveitis tend to be similar. In a recent study, the parents had a consanguineous relationship in 35 cases (26.1% of the total). There was a positive family history of the disease in 19 (12.8%) patients. Based on these findings, genetic factors play a significant role in disease development (10).

Various factors increase the risk of developing uveitis in JIA, including age at onset, gender, JIA subtype, and positivity for Anti-Nuclear Antibody (ANA). Studies indicate that girls with oligoarthritis and an early onset of JIA (under 7 years old) who are ANA-positive through immuno-fluorescence have the highest frequency of chronic anterior uveitis. In our study, at the time of diagnosis, uveitis was detected in 4 (2.6%) patients; of these cases, 3 patients had chronic anterior uveitis, and 1 patient had acute anterior uveitis. Four children were diagnosed with uveitis; three of them were girls and one was a boy. None of the patients diagnosed with uveitis had a positive ANA test result (6, 11).

The initial treatment approach for all patients (100%) under study involved using non-steroidal anti-inflammatory drugs. All of the patients received corticosteroid treatment, with 33.5% receiving pulse methylprednisolone for three consecutive days at a dosage of 30 mg/kg per day. Corticosteroids have been used as a bridge therapy in other studies as well. In this study, biologics including, etanercept, adalimumab, and infliximab were prescribed to approximately 10.7% of patients when other medications proved ineffective. This indicates a growing trend toward using these drugs as a suitable treatment option for JIA patients. Research, conducted globally in recent years, supports the increased use of biological drugs in JIA patients (12-14).

In this study, the excessive use of antibiotics before the first diagnosis of JIA suggests that the initial symptoms of the disease may be mistaken for septic arthritis and that the physicians may not be fully aware of the symptoms of JIA.

5- CONCLUSION

Juvenile idiopathic arthritis, like many other rheumatic diseases in children, may experience delays in diagnosis; because physicians may not have sufficient knowledge about this disorder. To effectively treat and manage this chronic childhood disease, it is essential to recognize its symptoms and clinical course. This report is the most extensive study on children with JIA in Northeast Iran. Understanding its prevalence and clinical manifestations in different regions and populations is crucial in making well-informed treatment decisions and improving the patients' health. Overall, the findings suggest that both immunogenic and environmental factors may play a crucial role in the prevalence of JIA subgroups among various ethnic groups.

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