JUVENILE ARTHRITIS DISEASE ACTIVITY SCORE IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS AND ITS ASSOCIATION WITH CLINICAL DISEASE ACTIVITY IN LAHORE

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ABSTRACT

Objective: To determine Juvenile Arthritis Disease Activity Score in children with juvenile idiopathic arthritis and its association with disease activity.

Study Design: Cross sectional analytical.

Place and Duration of Study: The study was conducted in the department of Immunology & Serology, the Children Hospital and the Institute of Child Health Lahore, from Jun 2015 to Jun 2016.

Material and Methods: All consecutive patients in a period of three months from June to August who fulfilled the inclusion criteria were enrolled from Out Patient Department and Medical Unit 1. Demographic profile including age and gender were recorded. Type of arthritis was assigned according to ILAR. The severity of the disease of patients was assessed by using the JADAS-27 score at the time of presentation. Statical analysis of data was done on SPSS version 17.0 for obtaining statistical results.

Results: Out of 45 patients, 44% (n=20) were males and 56% (n=25) were females between the age of 3-17 years. polyarthritis was found in 51.1% (n=23) followed by oligoarthritis 37.7% (n=17) and systemic onset disease 11.1% (n=5). Morning stiffness (97.8%) and fever (86.7%) were the most common clinical presentations. All patients with systemic onset disease had fever (n=5) followed by skin rash, hepatosplenomegaly and lymphadenopathy. C-reactive protein was positive in 30 (66.67%) patients. Erythrocyte sedimentation rate was raised in 41 (91.11%) patients. Rheumatoid factor (RF) positivity was observed in 12 (26.67%) cases. Anti-nuclear antibodies were found positive in 3 (6.66%) patients. Out of 45 patients 5 were in clinical remission, 11 were in minimal disease activity and 29 had severe clinical disease activity. Maximum 11 cases of severe disease activity lie between 30-40 JADAS-27 score each for CRP and ESR.

Conclusion: There was significant association between Juvenile Arthritis Disease Activity Score and Clinical Disease Activity. CRP and ESR were proved to be good inflammatory markers in JIA.

Keywords: CRP, ESR, Juvenile Arthritis disease, Activity score.

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is also known as Juvenile Rheumatoid Arthritis (JRA) describes a clinically heterogeneous group of arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks[1]. JIA is the most common chronic rheumatic disease in children and is an important cause of short and long-term disability[2]. JIA encompasses several disease categories; each has different modes of presentation, clinical signs, and symptoms, and in some cases, genetic background[3]. Its epidemiological studies reflect that JIA affects approximately 1 in 1,000 children in any given year, with about 1 in 10,000 having a more severe form worldwide. It commonly occurs in children from the age of 7 to 12, but it may occur in adolescents as old as 15 years of age, as well as in infants[4].

The prevalence of rheumatoid arthritis (RA) is reported to be 0.5-1% of world population[5]. It is the most prevalent disease, according to a recent study the incidence of JIA is approximately 13.9/100,000 children/year among children 15 years or younger, with an overall prevalence of approximately 113/100,000 children[6].

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Received: 21 Feb 2017; revised received: 08 Jul 2017; accepted: 11 Aug 2017

Researchers have identified changes in several genes that may influence the risk of developing juvenile rheumatoid arthritis. Many of these genes belong to a family of genes that provide instruction for making a group of related proteins called the human leukocytes antigen (HLA) complex. The HLA complex helps the immune system distinguish the bodies' own proteins from proteins made by foreign invaders (such as viruses and bacteria). Each HLA gene has many different normal variations, allowing each person's immune system to react a wide range of foreign proteins[7].

Sign and symptoms of JIA result from excessive inflammation in and around the joints. Inflammation occurs when the immune system sends signaling molecules and white blood cells to a site of injury or disease to fight microbial invaders and facilitate tissue repair. Normally, the body stops the inflammatory response after healing is complete to prevent damage to its own cells and tissues. Symptoms are often non-specific initially, and include lethargy, reduced physical activity, and poor appetite. The first manifestation, particularly in young children, may be limping. Children may also become quite ill, presenting with flu-like symptoms that persist the cardinal clinical feature is persistent swelling of the affected joint(s), which commonly include the knee, ankle, wrist and small joints of the hands and feet. Swelling may be difficult to detect clinically, especially for joints such as those of the spine, sacroiliac joints, shoulder, hip and jaw, where imaging techniques such as ultrasound or MRI are very useful. Pain is an important symptom. Morning stiffness that improves later in the day is a common feature. Late effects of arthritis include joint contracture (stiff, bent joint) and joint damage. Children with JIA vary in the degree to which they are affected by particular symptoms. Children may also have swollen joints[8].

Diagnosis of JIA is difficult because joint pain in children can be from many other causes. There is no single test that can confirm the diagnosis and most physicians use a combination of blood tests, x rays and the clinical presentation to make an initial diagnosis of JIA. The blood tests measure antibodies, Rheumatoid factor, and CRP, ESR and anti CCP antibodies. Unfortunately, the rheumatoid factor is not present in all children with JIA. So it is not a gold standard test to diagnosed rheumatoid arthritis in children. Moreover in some cases the blood work is somewhat normal. X-rays are done to ensure that the joint pain is not from a fracture, cancer, infection or a congenital abnormality. In most cases, fluid from joint aspirated and analyzed. This test often helps in making a diagnosis of JIA by ruling out other causes of joint pain[7]. The heterogeneous nature of JIA ensures that no single measure can reliably capture overall disease activity in all patients[8]. Systemic anti-inflammatory treatment with synthetic and/or biologic disease-modifying anti rheumatic drugs (DMARDs) is often required to achieve inactivity of arthritis[9].

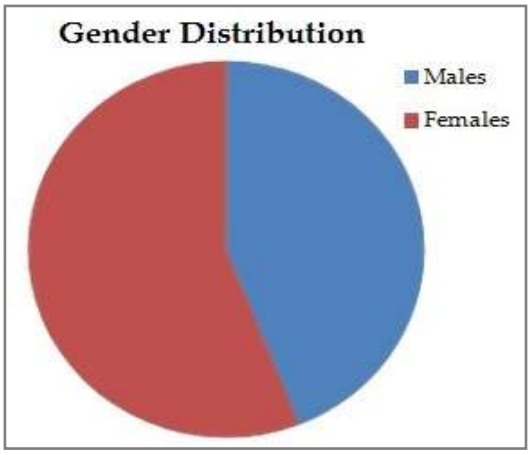

Figure: Gender distribution in the study population.

Juvenile Arthritis Disease Activity score 27 (JADAS-27) is a recently developed composite tool for scoring disease activity of (JIA). JADAS-27 consist of four items, the active joint count, the patient's/parent's global assessment and the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) as inflammatory markers, the total JADAS score ranging from 0-57[10]. The active joint count was taken from a total of 27 joints: Cervical spine, elbows, wrists, metacarpophalangeal joints (1, 2 & 3), proximal interphalangeal joints, hips, knees and ankle. ESR

tends to reflect disease activity of past few weeks where as CRP reflects more short term changes in disease activity. Furthermore, ESR can be influenced by confounding factors such as age, sex, fibrinogen levels, hypergammaglobulinemia, rheumatoid factor and anemia[11]. Levels of ESR range from 25-100mm/at the end of first hour by Westergen method in JIA patients[12]. Ther rationale of this study was to identify the association of juvenile arthritis disease score in children with juvenile idiopathic disease.

PATIENTS AND METHODS

This cross-sectional study was carried out in the department of Immunology & Serology, the Children Hospital and the Institute of Child Health, Lahore, over a period of 6 months, from June 2013 to December 2013. The study was conducted on 45 patients. All consecutive patients in period of three months from June to august who fulfilled the American college of Rheumatology (ACR) criteria of JIA were enrolled in the study. ACR criteria included age less than 16 years, signs of arthritis in one or more joints, disease duration 6 weeks or longer, onset type defined in first 6 months (i) Polyarthritis: when 5 or more inflamed joints; (ii) Oligoarthritis: when less than 5 joints and (iii) systemic onset disease: Arthritis with characteristic fever and exclusion of other forms of juvenile arthritis. Data collected include age, gender, number of joints involvement, and associated systemic features like morning stiffness, fever, rash, lymphadenopathy or hepatosplenomegaly. Venous blood sample was collected in clotted gel vial for CRP and in EDTA or sodium citrate containing vial for ESR.

For CRP measurement agglutination method was used in which sample and reagent (Human Tex CRP, Wiesbaden, and Germany LOT# 10032) used in 1:1 with positive and negative controls. Apositive reaction was indicated by a distinctly visible agglutination of latex particles indicated a CRP content of 6mg/L in non-diluted sample. If the sample gave positive reaction, then we went for semi-quantitative procedure. Done by using 1:1, 1:2, 1:4, 1:8, and 1:16 dilution. The highest dilution giving positive agglutination was the titer. For ESR determination Westergren method was used. Reagent (Tri Sodium citrate) and sample was used in 1:4. The normal value was 10-15mm/1st hour of reading. But in case of JIA these values lie up to 120mm/1st hour.

Statistical Analysis

Appropriate statistical data analysis technique by using SPSS 17.0 (Statistical package for social science) was applied. Distribution of patients in three types was described in percentages. Gender ratio was described. Mean age was determined and age distribution in various subgroups was determined to identify the most common age at presentation. Frequency and percentages of clinical features, laboratory parameters and drug treatment were made in three subtypes and described in tabulated form.

RESULTS

All the 45 patients with the age group from 3 to 17 years were enrolled in the study. The mean age ± SD of the patients under the study was 9.34 ± 3.409 years.

Out of 45 patients n=20 (44%) were males and n=25 (56%) were females and male to female ratio was 1:1.25.

Out of 45 known cases, 23 (51.1%) children had polyarthritis type of JIA out of which 8 (17.8%) cases were RAF positive and 15 (33.3%) cases were RAF negative. Seventeen (37.7%) cases were observed to have oligoarticular JIA and out of these 17 cases 11 (24.4%) were persistent and 6 (13.3%) were extended types of oligoarticular JIA. Five (11.1%) cases were positive for SOJIA (Systemic Onset JIA). None of the patients was observed to have psoriatic, enthesitis and undifferentiated categories of JIA (table-I).

Out of 45 cases, predominant clinical features were morning stiffness, joint pain, fever and joint deformities. Morning stiffness was observed in 44 (97.8%) children, 38 (84.4%) patients came with history of Joint pain, and 39 (86.7%) children had fever while 9 (20%)

children had deformities as well. Moreover 6 (13.3%) patients had skin rash, 6 (13.3%) and 3 (6.7%) patients were also observed to have hepatomegaly and splenomegaly respectively. Only 3 (6.7%) children with JIA had eye/uveitis (table-II).

Total number of patients was 45 out of which n=23 were of polyarticular JIA, n=17 were of Oligoarticular JIA and n=5 were of SOJIA. CRP was positive in 30 (66.67%) out of 45 patients, out of these 30 patients 17 (73.91%) were of polyarticular JIA, 8 (47.05%) positive were of oligoarticular JIA and 5 (100%) positive were of SOJIA. ESR was raised in 41 (91.11%) out of 45 patients, out of these 41 patients 22 (95.65%) were of polyarticular JIA, 14 (82.35%) were of Oligoarticular JIA and 5 (100%) cases were of SOJIA. Rheumatoid factor (RF) positivity was observed in 12 (26.67%) out of 45 cases and out of these 12 cases, 8 (34.78%) patients were of polyarticular JIA, 1 (5.88%) was of oligoarticular JIA and 3 (60%) cases were of systemic onset types of JIA. Anti-nuclear antibodies were found positive in 3 (6.66%) out of 45 patients, out of these 3 patients 2 (8.69%) children were of polyarticular JIA and 1 (20%) patient was of SOJIA. No one from oligoarticular JIA was found positive for ANA (table-III).

There was a significant association between JDAS27-CRP and JDAS27-ESR with severity of disease. Clinical remission, minimal disease activity and severe disease activity were associated with JADAS27-CRP and JADAS27-ESR. This showed that 5 cases out of 45 were in clinical remission and they lie in the range of <10 JADAS-27 scoring each for CRP and ESR. Eleven patients were in minimal disease activity and 29 patients had severe clinical disease activity. Maximum 11 cases of severe disease activity lie between 30-40 JADAS-27 score each for CRP and ESR. About n=5 (11.1%) were in clinical remission, n=11 (24.4%) were in minimal disease

Table-I: Age distribution in the study population.

	Minimum	Maximum	Mean	SD
Age	3	17	9.34	3.409

Table-II: Frequency of types of Juvenile Idiopathic Arthritis (JIA) in study population.

Type	Total	Sub types	Frequency	Percentage
Polyarthritis	23 (51.1%)	RAF +ve	8	17.8
		RAF-ve	15	33.3
Oligoarthritis	17 (37.7%)	Persistent	11	24.4
		Extended	6	13.3
Systemic Disease	5 (11.1%)	Yes	5	11.1
		No	40	88.9
Other Categories	0 (0%)	Psoriatic	0	0
		Enthesitis	0	0
		Undifferentiated	0	0

Table-III: Frequency of Clinical Features in study population.

Clinical Features	Yes	No
Morning Stiffness	44 (97.8%)	1 (2.2%)
Joint Pain	38 (84.4%)	7 (15.6%)
Fever	39 (86.7%)	6 (13.3%)
Rash	6 (13.3%)	39 (86.7%)
Deformities	9 (20%)	36 (80%)
Hepatomegaly	6 (13.3%)	39 (86.7%)
Splenomegaly	3 (6.7%)	42 (93.3%)
Eye/Uveitis	3 (6.7%)	42 (93.3%)

activity and n=29 (64.4%) were in severe disease activity (table-IV).

DISCUSSION

Juvenile Idiopathic Arthritis (JIA) also known as Juvenile Rheumatoid Arthritis (JRA) is the most common form of arthritis in children and adolescents. Reviews of 34 epidemiological studies showed that 0.07-4.01 per 1000 children worldwide are affected. The true incidence and prevalence in our country is not known. Published data are difficult to compare because of varying referral patterns, the heterogeneity of disease, its evolution over time, differences in classification criteria, dissimilarity of source population. Substantial geographic and ethnic differences are present with regard to age at onset, relative frequencies of onset types and immunological markers.

In the Western literature, the most frequently reported age of onset of JRA is 1-3 years and it is more common in female as compared to male[13]. In his study and many regional studies, males were either equal or more in number as compared to females. Similarly, late age at presentation was seen in this study as well as from another Pakistani study and various Indian studies. The reason may be the ethnic and geographic similarity of both populations, or biological characteristic of the disease in this subcontinent. Another reason may be male gender prominence in South East Asians where females are given less importance and usually not brought to the hospital. This is true as all were hospital based studies[14]. Different scenario in a community based study in Bangladesh where female to male ratio was equal in polyarticular JIA.

Table-IV: Laboratory Parameters in JIA Subtypes.

	Polyarthritis (n=23)	Oligoarthritis (n=17)	Systemic Onset (n=5)	Total (n=45)
CRP Positivity	17	8	5	30
ESR >20mm Hg	22	14	5	41
RF Positivity	8	1	3	12
ANA Positivity	2	0	1	3

Table-V: Association of Disease severity with JADAS-27 Score.

Score Range	Association Wit Severity of Disease					
	Clinical Remission		Minimal Disease Activity		No Remission/Severe Disease Activity	
	JADAS 27-CRP	JADAS 27-ESR	JADAS 27-CRP	JADAS 27-ESR	JADAS 27-CRP	JADAS 27-ESR
<10	5	5	2	4	0	0
10-20	0	0	8	6	0	1
20-30	0	0	1	1	10	8
30-40	0	0	0	0	11	11
40-50	0	0	0	0	5	6
50-60	0	0	0	0	3	3
Total	5	5	11	11	29	29

In our study we observed that signs and symptoms of JIA resulted from excessive inflammation in and around the joints. These signs and symptoms coincided with a study conducted by Hoffart and Sherry[14]. Symptoms were often non-specific initially, and include lethargy, reduced physical activity, and poor appetite. The first manifestation, particularly in young children, may be limping. Children may also become quite ill, presenting with flu-like symptoms that persist[15]. The cardinal clinical

feature was persistent swelling of the affected joint(s), which commonly include the Knee, ankle, wrist and small joints of the hands and feet. Swelling may be difficult to detect clinically, especially for joints such as those of the spine, sacroiliac joints, shoulder, hip and jaw, where imaging techniques such as ultrasound or MRI are very useful. Pain is an important symptom. Morning stiffness that improves later in the day is a common feature. Late effects of arthritis include joint contracture (stiff, bent joint) and joint damage. Children with JIA vary in the degree to which they are affected by particular symptoms. Children may also have swollen joints. Juvenile Arthritis Disease Activity Score 27 (JADAS-27) is a major scoring system for evaluating disease activity of juvenile idiopathic arthritis[15].

Ringold and Singer, (2008) performed the similar study and published in current rheumatology views. He concluded that JADAS is a quantitative measure of disease activity used to monitor the disease activity of rheumatoid arthritis[16]. It is calculated using a formula that includes the number of tender joints and swollen joints (27 joints maximum). JADA-27 is not only useful for assessing patients in clinical practice but for clinical trials as well. This measure disease burden using patient global health (patient self-assessment), tender joint-counts and swollen joint-counts (up to 27), and the ESR or CRP.

CONCLUSION

In this study we concluded that there was a significant association between juvenile arthritis disease activity score and clinical disease activity. CRP and ESR are proved to be good inflammatory markers in JIA.

Ethical Considerations

Confidentiality of information will be ensured.

RECOMMENDATIONS

On the basis of results, it should be suggested that

- JADAS27-CRP and JDAS27-ESR should be associated with disease severity in clinical practice.
- Its confirm diagnosis should be accompanied by the determination of serum levels of anti-CCP Antibodies.

Budget of the Research

This Research will not be funded by the School of Allied Health Sciences (CH & ICH), Lahore or any other organization.

ACKNOWLEDGMENT

We are grateful to the Rheumatology Department, Associate Professor, Immunology Department Dr Farhana Shahzad institute of child and health Lahore, Principle of SAHS and staff of Immunology Department for allowing and helping us to complete this work.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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