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Original Research Article

A study on disease activity and outcome in patients with juvenile idiopathic arthritis, aged 2 months to 16 years at a tertiary care institute in North India and compare JADA'S based on ESR to JADA'S based on CRP in newly diagnosed patients

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ABSTRACT

Background: Juvenile idiopathic arthritis is the most common chronic rheumatic disease of childhood. The clinical spectrum spans from time-limited mono-arthritis to ongoing aggressive poly-articular disease, and may include severe systemic features or sight-threatening uveitis.
Methods: This was a prospective 2 years study conducted from September 2018 to August 2020 in the Department of Pediatrics, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, a tertiary care institute in North India. Patients were assessed individually by interview and clinical examination supported by Laboratory investigations. Patients were diagnosed and assigned to different JIA categories based on ILAR classification. Disease Activity and Outcome was measured based on JADAS-27.
Results: A total of 51 patients were enrolled in our study, based on inclusion and exclusion criteria. The most common clinical features in studied subjects were: joint pain and swelling each found in 48 (94.1%) patients, restricted joint movement found in 42 (82.3%) patients, limp found in 36 (70.5%) patients, fever in 9 (17.6%) patients, rash in 6 (11.8%) patients and joint deformity in 3 (5.9%) patients. Of the 51 patients, 24 (47%) patients had no change in disease activity, 24 (47%) improved with significant reduction in disease activity and 3 (6%) patients worsened with increased disease activity during the course of study.
Conclusions: Oligorthritis was the most common subtype of JIA observed. Joint pain and swelling were the most common presentations. Knee, ankle and hip joints were the most commonly involved joints. Disease activity was mostly moderate to high initially. Maximum improvement in disease activity on follow up was observed in oligorthritis persistent variant.

Keywords: Disease activity, Juvenile idiopathic arthritis, Juvenile arthritis disease activity score

INTRODUCTION

Juvenile idiopathic arthritis is, according to the International league against rheumatism (ILAR), defined as swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness, which persists for at least 6 weeks in a child under 16 years of age, observed by a physician, and not due to primarily mechanical disorders or to other identifiable causes.[1]

Juvenile idiopathic arthritis is the most common chronic rheumatic disease of childhood.[2] The clinical spectrum spans from time-limited mono-arthritis to ongoing aggressive poly-articular disease, and may include severe systemic features or sight-threatening uveitis. The broad spectrum in symptoms and signs, clinical findings and course, implies that JIA is probably not one specific disease, but rather a group of disease entities. There is no simple diagnostic test but the diagnosis of JIA is based on a combination of clinical findings, duration and exclusion of other conditions. The term JIA is still used for adult patients that have had juvenile onset of a chronic idiopathic arthritis. The varying definitions used in different time periods and parts of the world may partly explain the diverging results both in incidence and disease outcome in studies of chronic childhood arthritis. The universal acceptance of the ILAR classification criteria for JIA is a giant step forward and an important prerequisite to gain new and valid knowledge on the disease.[3,4]

It seems clear that JIA is a multi-factorial disease, although etiology remains largely unknown.[5] There is strong evidence of genetic factors conferring an overall susceptibility to JIA.[6]

The human major histocompatibility complex (MHC) plays an important role in the body's recognition of self, and it is closely linked to autoimmunity. Associations with multiple MHC-class II molecules and with specific genes have been shown for certain categories of JIA.

A sequence of triggering events preceding onset of JIA in a genetically predisposed individual seems likely. Environmental factors as infections and vaccinations have been suggested as triggers of onset and relapses in JIA, but no single trigger has been identified.[7]

Symptoms and clinical findings

A limp and morning stiffness, joint swelling, pain and restricted movement in one or more joints are the most common symptoms and clinical findings at onset of JIA.[8] General malaise, fever and exanthema may occur.[9] While localized symptoms as joint stiffness and pain dominates in older children, general symptoms appetite, irritability and increased need for rest and disturbed sleep may characterize the onset in in early chidhood.[10] Blood tests may be normal, but unspecific markers of inflammation as anemia, thrombo-cytosis, raised ESR and/or CRP are common findings. Specific immunological markers as ANA, RF, ACPA and HLA-B27 may be found, but are not a prerequisite for the diagnosis and is not present in many children with JIA.[11]

Outcome

JIA may have considerable impact on growth and development, physical and psychosocial functioning. There is a wide range of potential consequences, and therefore no single measure of outcome. Knowledge on the long-term outcome of JIA is important to guide treatment, for information to the individual child and family, and for the society in providing health services.[12] Outcome can be defined as consequences of the disease process over time. Strictly speaking, outcome can be described precisely only at the end of the disease process, still both short- and long-term studies provide valuable information. Robust definitions of disease activity, remission and other standardized outcome measures are essential so that outcome studies can be compared.[13]

Outcome studies show inconsistent and conflicting results, and reflect methodological problems such as study design, study population and method of case accrual.[12] In most studies the number of patients in each category is low, so the category-specific results must be interpreted with caution. Hospital-based studies from tertiary pediatric or adult rheumatology centers will evaluate a selected cohort with an outcome that may differ from population-based studies. On the other hand, cross-sectional studies miss fluctuations in disease activity over time, and cannot measure sustained clinical remission off treatment.[14] Disease activity should therefore be assessed over time to avoid underestimation of duration and chronicity of the disease.

Simple measures of disease activity are; the number of inflamed joints, tender joints, joints with restricted movement, inflammatory markers and visual analogue scales of pain, and global assessment of disease severity. Among these physicians' global assessment of disease activity and active arthritis joint counts show high correlation to other measures of disease activity and has a high responsiveness to change.[15] A composite disease activity score combining four of these simple measures known as juvenile arthritis disease activity score (JADAS) was recently developed and validated.16 juvenile arthritis disease activity score (JADAS) includes the following measures;

- Number of joints with active arthritis assessed in 10, 27 or 71 joints, depending on whether 10 or 27 reduced joint count is 71 full joint count is used.
- Parent/patient's global assessment of well-being,
- Physician's global assessment of disease activity, and
- ESR.

The sum of these four components yields a number on a continuous scale to quantify disease activity.

Hence, we decided to study the Disease Activity and Outcome in children with JIA, aged 2 months to 16 years, based on JADAS and also to compare JADAS with either ESR or CRP at admission and on follow up after 1 year.

METHODS

The study was conducted in the Department of Pediatrics, Sher-i-Kashmir Institute of Medical Sciences (SKIMS),

Srinagar, a tertiary care institute in North India. Patients were recruited from Departments of Pediatrics and Department of Rheumatology SKIMS Soura. Study was explained to patients and proper consent was taken from them.

Inclusion criteria

All patients with a diagnosis of Juvenile Idiopathic Arthritis according to the ILAR criteria within the study period with minimum age of 2 months and maximum age of 16 years. The requirement for continued inclusion into the study was at least 2 registered visits, including the baseline visit and a follow up visit after 1 year.

Exclusion criteria

Patients with age below 2 months and above 16 years. Patients who refuse to give consent. Who cannot be followed up.

Study methods

This was a prospective 2 years study conducted from September 2018 to August 2020. Patients were assessed individually by interview and clinical examination. Laboratory investigations including baseline investigations like CBC, VBG, Electrolytes, KFT, LFT and disease specific investigations including ESR, CRP, RF, ANA and anti-CCP were done. Patients were diagnosed and assigned to different JIA categories based on ILAR classification. Disease Activity and Outcome was measured based on JADAS-27 using following measures: 1) physician global assessment of disease activity, which is a subjective interpretation of patient's overall status measured on a horizontal 10cm Visual Analgoue Scale (VAS) [0=Best, 10=Worst], 2) patient/parent global assessment of overall wellbeing, which employs a validated 10cm VAS [0=Best, 10= Worst], 3) Active Joint Counts. (from a total of 27 joints) and 4) ESR and CRP normalized to 0-10 by formula (ESR-20)/10 and (CRP-10)/10, with ESR <20 given a value of 0, ESR >120 given a value of 10 and CRP <10 given a value of 0 and CRP >110 given a value of 10.

Juvenile arthritis disease activity score-27 (JADAS-27) of each patient was calculated based on ESR and CRP and comparisons were made between JADAS 27 based on ESR and JADAS 27 based on CRP. Patients were re-assessed after 1 year of follow up.

Several versions of JADAS are available including JADAS-71, JADAS-27 and JADAS-10, depending on whether the whole 71-joint count is used or reduced 27 or 10 joints count is used.

We used JADAS-27 in our study. The JADAS-27 includes a selected count of the following joints: cervical spine, elbows, wrists, metacarpophalangeal joints (from first to third), proximal interphalangeal joints, hips, knees and ankles.

It yields a score ranging from 0-57. Disease activity is classified into inactive disease, low disease activity, moderate disease activity and high disease activity based on the following cut off values.[7,9]

Oligoarthritis

Oligoarthritis as inactive disease ≤1, low disease activity 1.1-2, moderate disease activity 2.1-4.2 and high disease activity >4.2.

Polyarthritis

Polyarthritis has inactive disease ≤1, low disease activity 1.1-3.8, moderate disease activity 3.9-8.5 and high disease activity >8.5.

Data analysis

After collection of data, data was subject to analysis with appropriate statistical methods for dependent and independent variable notably the chi square test and fisher's exact test. P values <0.05 were considered significant.

RESULTS

Age distribution

We enrolled a total of 51 patients in our study, based on inclusion and exclusion criteria. The minimum age of presentation was 3 years, maximum age was 16 years and average age was 11 years ±4.37 SD.

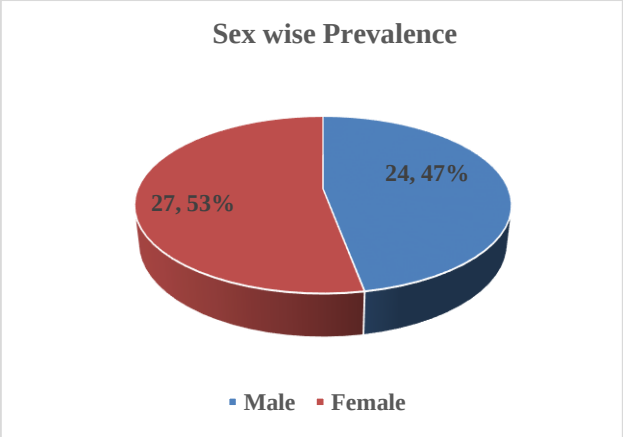

Figure 1: Sex distribution.

Sex distribution

Of the 51 patients, 27 (53%) were females and 24 (47%) were males, with female to male ratio of 1.1.

Clinical features

The most common clinical features in studied subjects were: Joint pain and swelling each found in 48 (94.1%) patients, restricted joint movement found in 42 (82.3%) patients, limp found in 36 (70.5%) patients, fever in 9 (17.6%) patients, rash in 4 (11.8%) patients and Joint deformity in 3 (5.9%) patients.

Table 1: Distribution of clinical features.

Clinical features	No. of patients	Percentage
Joint pain	48	94.1%
Joint swelling	48	94.1%
Restricted joint movement	42	82.3%
Limp	36	70.5%
Fever	9	17.6%
Rash	6	11.8%
Joint deformity	3	5.9%

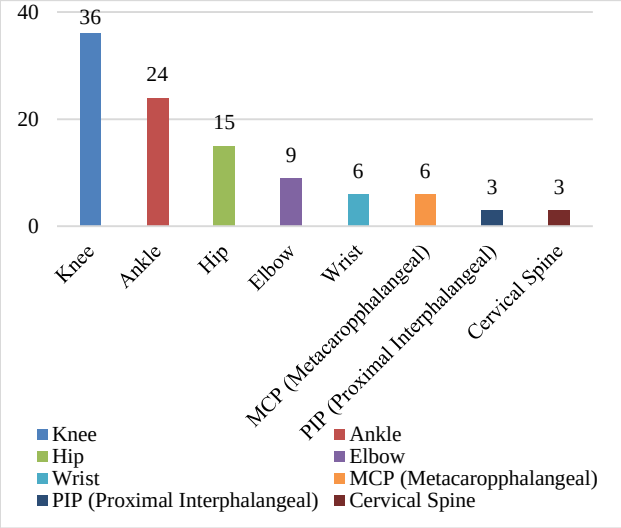

Figure 2: Joint involvements in JIA in studied subjects.

Joint involvement

The most commonly involved joints among study subjects were - knee in 36 (70.5%) patients, ankle in 24 (47.1%) patients, hip in 15 (29.4%) patients, elbow in 9 (17.6%) patients, wrist and metacarpophalangeal joints each in 6 (11.8%), proximal interphalangeal joints and cervical spine each in 3 (5.9%) patients.

Inflammatory markers

Among the inflammatory markers studied, high ESR (>20mm/h) was found in 45 (88.2%) patients, CRP was positive (>10 mg/l) was found in 42 (82.4%) patients, ANA was positive in 6 (11.8%) patients and RF was positive in 6 (11.8%) patients.

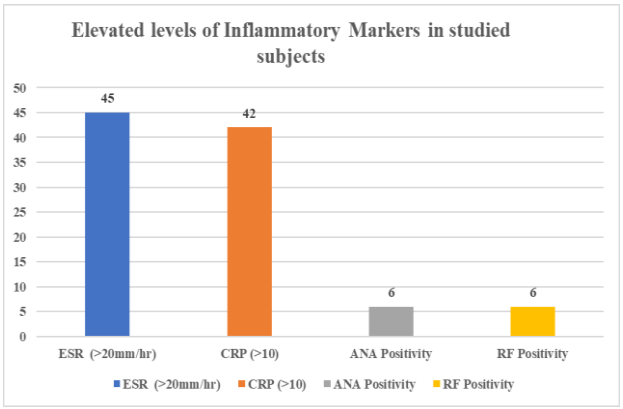

Figure 3: Inflammatory markers in studied subjects.

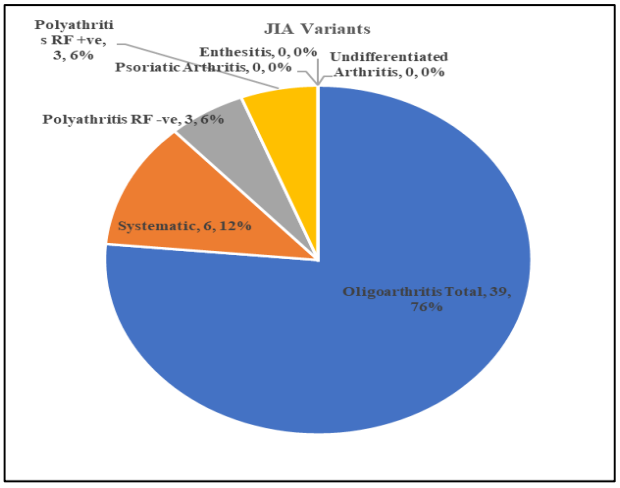

Figure 4: JIA categories in studied patients.

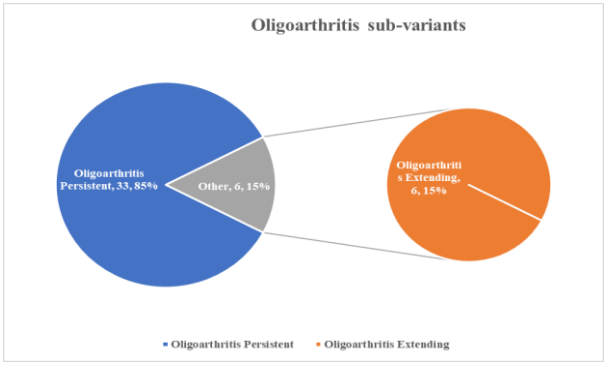

Figure 5: Oligoarthritis sub-variants.

JIA category distribution

Of the 51 patients, 39(76.5%) patients belonged to oligoarthritis, of which 33 (64.7%) had oligoarthritis persistent and 6 (11.8%) had oligoarthritis extending, 6 (11.8%) belonged to systemic arthritis, 3 (5.9%) patients belonged to each polyarthritis RF negative and polyarthritis RF positive. We had no patients belonging to psoriatic arthritis, enthesitis related arthritis and undifferentiated arthritis.

Disease activity (based on JADAS-27) at initial visit

On first visit, of the total 51 patients, 3(5.9%) had low disease activity, 21 (41.1%) had moderate disease activity, 27 (52.9%) had high disease activity and no patient had inactive disease.

Of the 39 patients belonging to oligoarthritis, 3 (7.7%) had low disease activity, 21 (53.8%) had moderate disease activity, 15 (38.4%) had high disease activity. Remaining 12 patients belonging to systemic arthritis, polyarthritis RF negative and polyarthritis RF positive had high disease activity.

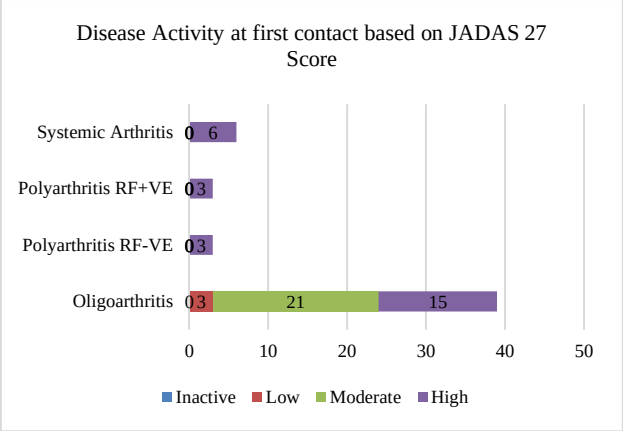

Figure 6: Disease activity at first contact in patients based on JADAS-27.

Table 2: Disease activity at follows up in studied patients based on JADAS-27 Score.

JIA category	Disease activity (%)				Total (%)
	Inactive	Low	Moderate	High	
Oligoarthritis	6 (15.3)	9 (23.0)	18 (46.1)	6 (15.3)	39 (76.5)
Polyarthrits (RF Negative)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)	3 (5.9)
Polyarthrits (RF Positive)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)	3 (5.9)
Systemic Arthritis	0 (0.0)	0 (0.0)	0 (0.0)	6 (100.0)	(11.8)
Total	6 (11.7)	9 (17.6)	18 (35.2)	18 (35.2)	51 (100.0)

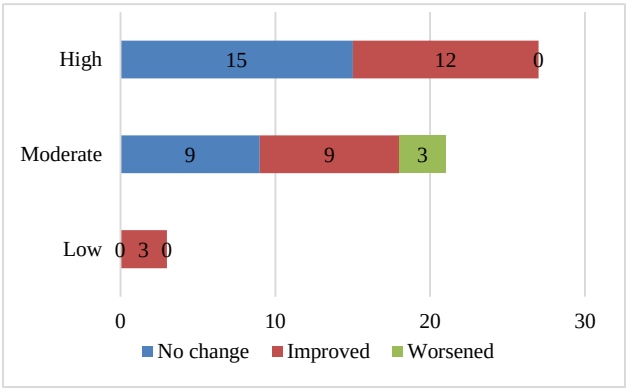

Figure 7: Change in disease activity during the course of study.

Table 3: Comparison of JADAS-27 ESR with JADAS-27 CRP.

Particulars	JADAS 27 ESR	JADAS 27 CRP	P value
Pearson corelation	1	1.00	<0.0001

Correlation is significant at the 0.01 level (2-tailed).

Disease activity on follows up visit after 1 year

On follow up visit 1 year after the initial contact, of the total 51 patients, 6(11.7%) had inactive disease, 9 (17.6%) had low disease activity, 18 (35.2%) had moderate disease activity and 18 (35.2%) had high disease activity.

Of the 39 patients belonging to oligoarthritis, 6 (15.3%) had inactive disease, 9 (23%) had low disease activity, 18 (46.1%) had moderate disease activity and 6 (15.3%) had high disease activity. The remaining 12 patients, 6 systemic arthritis, 3 polyarthritis rf negative and 3 polyarthritis rf positive had high disease activity.

Change in disease activity during the course of study

Of the 51 patients, 24 (47%) patients had no change in disease activity, 24 (47%) improved with significant reduction in disease activity and 3 (6%) patients worsened with increased disease activity during the course of study.

One patient with low disease activity on first visit improved with inactive disease on follow up. of the 21 patients with moderate disease activity on initial visit, 9 (42.8%) had no change in disease activity, 9 (42.8%) improved and 3 (14.3%) worsened with increased disease activity on follow up. Of the 27 patients with high initial disease activity, 15 (55.5%) had no change in disease activity, 12 (44.4%) improved with significant reduction in disease activity on follow up.

Comparison of JADAS-27 ESR and JADAS-27 CRP

JADAS-27 ESR and JADAS-27 CRP was calculated in all 51 patients both on initial and follow up visit and results were compared. We found a close correlation

between the two with P value less than 0.0001 (significant) and Pearson correlation coefficient of 1.

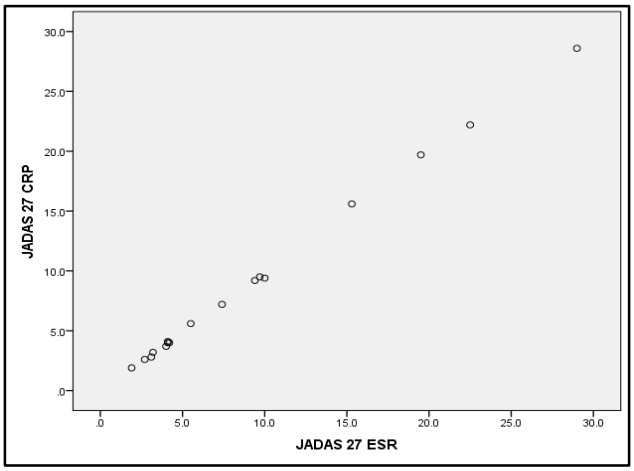

Figure 8: Comparison of JADAS-27 ESR with JADAS-27 CRP.

DISCUSSION

Juvenile idiopathic arthritis is the most common chronic rheumatic disease of childhood.17 Juvenile arthritis disease activity score (JADAS) is a recently developed composite tool for measuring disease activity in patients with JIA. It is based on linear sum of 4 outcome variables of JIA viz. Physician's global assessment of disease activity, patient/parent global assessment of overall well-being, active joint count and ESR. Several versions of JADAS are available including JASAS-71, JADAS-27 and JADAS-10 based on the joint count used. We used JADAS-27 in our study

In our study, the minimum age of presentation was 3 years, maximum age was 16 years and average age was 11 years. This is similar to other Indian and Asian studies.[18-20] Where a higher average age of presentation has been seen compared to Western studies where lower age of presentation is seen.[21] In a study conducted by Shahzad et al, age of presentation was 3-17 years with average age of 9.34 years.[18]

In our study, 27 (53%) patients were females and 24 (47%) were males with male to female ratio of 1:1.1.

Joint pain and swelling were the most common clinical presentation in our study observed in 48 (94.1%) patients, Restricted Joint movement was seen in 42 (82.3%) patients, Limp in 36 (70.5%) patients, fever in 9 (17.6%) patients, Rash in 6 (11.8%) patients and Joint deformity in 3 (5.9%) patients. Our results are comparable to those in study done by Hedge et al and other Indian studies.[22]

The most commonly involved joints in our study were: knee in 36 (70.5%) patients, ankle in 24 (47.1%) patients, hip in 15 (29.4%) patients, elbow in 9 (17.6%) patients, wrist and metacarpophalangeal (MCP) joints each in 6 (11.8%) patients, proximal interphalangeal joints (PIP) and cervical spine each in 3 (5.9%) patients. Our results are comparable to those observed by Aggarwal et al and Hedge et al and in other Indian studies.[22,23] In the study done by Aggarwal et al, among children with pauciarticular disease, ankle (75%) and knee (63%) were the most frequently involved joints, followed by sacroiliac (38%), wrist (28%), hip (26%), cervical spine (10%), elbow and shoulders. In polyarticular disease, the joints involved were knees (87%), ankle (85%), wrist (81%), small joints of hands (69%), elbow (68%), shoulder (57%), hips (22%) and temporomandibular joint (5%).[23] The joints involved in systemic onset JIA were wrist (66%), elbow (58%), knee (60%), ankle (50%), small joints of hands (42%). In the study done by Hedge et al knee joint was most frequently involved joint, followed by wrist, ankle, small joints of hands, and elbows, in that order.[22]

In our study, ESR was raised (>20mm/h) in 45 (88.2%) patients, CRP was positive (>10 mg/l) in 42 (82.4%) patients, ANA was positive in 6 (11.8%) patients and RF was positive in 6 (11.8%) patients, which is comparable to the study done by Shahzad et al where in ESR was raised in 91.11% patients, CRP was positive in 66.67% patients, ANA was positive in 6.66% patients and RF was positive in 26.67% patients.[23]

Oligoarthritis was the most common subtype of JIA in our study observed in 39 (76.5%) patients with 33 (64.7%) having oligoarthritis persistent and 6 (11.8%) having oligoarthritis extending type JIA. Systemic arthritis was seen in 6 (11.8%) patients and polyarthritis was found in 6 (11.8%) patients with 3 (5.9%) belonging each to RF positive and RF negative subtypes. We had no patients with psoriatic arthritis, enthesitis related arthritis and undifferentiated arthritis, may be due to smaller sample size.

In our study, at initial visit, 5.9% patients had low disease activity, 41.1% had moderate disease activity, 52.9% had high disease activity and no patient had Inactive disease. Of the 39 patients belonging to oligoarthritis, 7.7% had low disease activity 53.8% had moderate disease activity, 38.4% had high disease activity. Remaining 12 patients belonging to systemic and polyarthritis RF negative and polyarthritis RF positive had high disease activity.

On follow up visit 1 year after recruitment, 11.7% patients had inactive disease, 17.6% patients had low disease activity, 35.2% patients had moderate disease activity and 35.2% patients had high disease activity. Of the 39 patients belonging to oligoarthritis, 15.3% patients had inactive disease, 23% patients had low disease activity, 46.1% patients had moderate disease activity and 15.3% patients had high disease activity. The remaining 12 patients, 6 systemic arthritis, 3 polyarthritis RF negative and 3 polyarthritis RF positive continued to have high disease activity on follow up.

Thus, at follow up, 47% patients had no change in disease activity, 47% patients improved with significant reduction in disease activity and 6% patient worsened with increased disease activity during the course of study.

3 patients with low disease activity on first visit improved with inactive disease on follow up. of the 21 patients with moderate disease activity on initial visit, 42.8% patients had no change in disease activity, 42.8% patients improved and 14.3% worsened with increased disease activity on follow up. Of the 27 patients with high initial disease activity, 55.5% patients had no change in disease activity and 44.4% patients improved with significant reduction in disease activity on follow up. The disease activity was calculated based on JADAS-27.

Similar to our study, Shahzad et al conducted a study on disease activity in JIA patients based on JADAS-27, of the 45 patients, 5 (11.1%) were in clinical remission (Inactive disease), 11 (24.4%) had minimal disease activity and 29 (64.4%) had severe clinical disease activity.

In our study, improvement in disease activity was observed mostly in oligoarthritic persistent variant. Since patients were followed up for 1 year after initial visit, further follow up is needed to notice any significant improvement in disease activity in other patients.

We also used CRP to calculate JADAS-27 scores in each patient both on initial visit and follow up and then compared the results with JADAS-27 based on ESR. We found a close correlation between JADAS based on ESR with JADAS based on CRP with p-value <0.0005. Our results are consistent with observations of Nordal et al where they found a close correlation between JADAS based on CRP with JADAS based on ESR.[4] Thus, CRP can be used to replace ESR for calculation of JADAS, CRP being more feasible and easily available than ESR and can be done on skin prick compared to ESR requiring venipuncture.

Limitations

Since we could do follow up for 1 year only, more recruitment and follow up is needed to define figures more appropriately.

CONCLUSION

Oligorthritis was the most common subtype of JIA observed. Joint pain and swelling were the most common presentations. Knee, ankle and hip joints were the most commonly involved joints. ESR and CRP were raised in most patients. ANA and RF were positive only in small fraction of patients. Disease activity was mostly moderate to high initially. Maximum improvement in in disease activity on follow up was observed in oligorthritis persistent variant. JADAS based on CRP correlated closely with JADAS based on ESR, thus CRP can be used instead of ESR for calculation of disease activity based on JADAS, CRP being more feasible, readily available than ESR.

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