

Study of Serological and Clinical Factors among Juvenile Rheumatoid Arthritis Cases admitted to Mofid Children's Hospital and Imam Hossein Hospital, Tehran, IRAN

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INTRODUCTION AND AIM: Juvenile Rheumatoid Arthritis is the most common rheumatologic disease of childhood period. The aim of study was to compare ANA positive and ANA negative cases.

PATIENTS AND METHODS: This observation study was performed as correlation research. All cases with diagnosis of JRA who visited Mofid Children's Hospital and Imam Hossein Hospital were included in this study. Duration of this study was from 2006, 1 October till 2008, 31 October. All patients were examined carefully by an experienced pediatric rheumatologist. Age, sex, disease onset, age at diagnosis, RF, ANA, HLA-B27, ESR, type of disease, disease activity, and duration of inactivity were included in this study. ANA titer was measured by immunofluorescence technique. Patients were categorized according to sex, ANA, and type of disease and then group was compared with each other. Data was analyzed by SPSS Ver.16 (Chicago, IL, USA). This study was approved by Ethical Committee of university.

RESULTS: In this study, 61 cases were enrolled. Twenty five cases (41%) were males and 36 cases were females. Mean of age at disease onset was 6.1 ± 3.1 (Range 6 months to 12.5 years). Mean of age at disease diagnosis was 6.7 ± 3.2 . Mean of age at time of study was 7.6 ± 3.5 (1.4 to 14 years). From all cases, 38 cases were oligoarticular, 18 cases were polyarticular and 5 cases were systemic onset. From 61 cases, 22 (36.1%) cases, had ANA positive JRA. Of these cases, 14 cases were oligoarticular and 8 cases were polyarticular.

CONCLUSION: Except for sex and morning stiffness, there is significant correlation between type of disease and ANA, RF, HLA-B27, response to treatment, early onset erosion, subcutaneous nodule, and uveitis ($P < 0.05$). There is significant correlation between sex and ANA, RF, HLA-B27, early erosion, response to treatment, subcutaneous treatment, and uveitis ($P < 0.05$). There is significant correlation between ANA seropositivity and HLA-B27, early erosion, response to treatment, uveitis and subcutaneous nodule. Our results showed that there is significant correlation among ANA and other factors except morning stiffness. Another prospective study is recommended.

KEYWORDS: Antinuclear Antibodies, Juvenile Rheumatoid Arthritis, Morning Stiffness, Rheumatoid Factor, HLA-B27, Subcutaneous nodule

INTRODUCTION AND AIM: Juvenile idiopathic arthritis (JIA) or Juvenile rheumatoid arthritis (JRA) is the most common rheumatic disorder of childhood with a prevalence between 7 and 400 per 100,000 children. Seven subgroups of JIA have been defined by the International League of Association for Rheumatology (ILAR), with oligoarticular JIA being the most common. Although in western European countries the most common subtypes is represented by oligoarthritis, this same subtypes is rare in countries such as Costa Rica, India, New Zealand, and South Africa, where polyarthritis predominates. Several indicators of poor outcome have been identified, including greater severity or extension of arthritis at onset, symmetrical disease, early wrist or hip involvement, presence of RF, persistent of active disease. The aim of this study was to compare ANA positive and ANA negative cases.

PATIENTS AND METHODS: All cases with diagnosis of JRA who visited Mofid Children's Hospital and Imam Hosein Hospital were included in this study. We used ACR criteria for diagnosis of JRA in this study. Duration of this study was from 2006, 1, Oct till 2008, 31, Oct. Cases without ANA test were excluded from our study. Patients who changed their diagnosis and patients who didn't complete follow-up were excluded from our study. All patients were examined carefully by a pediatric rheumatologist. Age, sex, disease onset, age at diagnosis, RF, ANA, HLA-B27, ESR, type of disease, disease activity, and duration of inactivity were included in this study. ANA titer was measured by immunofluorescence technique. Slit lamp examination was used to detect uveitis. Data was analyzed by SPSS Ver.16 (SPSS Inc; Chicago, IL, USA) and EPI-info. Chi-square test, Fisher-exact test, and independent sample t-test were used for analysis. This study was approved by Ethical Committee of university.

RESULTS: In this study, 61 cases were enrolled. Twenty five cases (41%) were males and 36 cases were females. Mean of age at disease onset was 6.1 ± 3.1 (Range 6 months to 12.5 years). Mean of age at disease diagnosis was 6.7 ± 3.2 . Mean of age at time of study was

7.6±3.5 (1.4 to 14 years). Mean ±SD of ESR among ANA positive and ANA negative groups was 47.68±27.31 and 60.05±37.84 respectively(P=0.04). ANA was positive in 14(38.84%) cases with oligoarticular and 8(44.44% of polyarticular cases(P=0.03). RF was positive in 22.22% of polyarticular cases versus 5.55% of oligoarticular cases(P<0.0001)(Table-1). Uveitis was seen only in oligoarticular type of disease(P<0.0001)(Table-1). Response to treatment was positive in 30(78.94%) of Oligoarticular, 11(61.11%) of polyarticular, and 5(100%) of systemic onset disease.(P<0.0001). As shown in table 2, Mean±SD of ESR was significantly higher in male(73.04±34.17 vs. 43.83±30.07). HLA-

B27 was positive in 21.73% of males and 5.55% of females(P<0.0001). Early erosion was seen in 17.39% of males and 8.57% of females(P<0.0001). (Table-2)

Morning stiffness was more frequent in ANA positive cases(61.9%) compared to ANA negative cases(47.36%). Rate of response to treatment was higher among ANA negative cases(89.74%) compared to ANA positive cases(50.00%)(P<0.001). ESR in ANA negative cases was higher than ANA positive cases(60.05±37.845 vs. 47.68±27.32)(P=0.04). Uveitis was more frequently seen in ANA positive cases (27.27% vs. 2.56%). (Table-3)

Table-1: Serological and Clinical Features among different Types of JRA

Type of Disease		Oligoarticular (n=38)	Polyarticular (n=18)	Systemic (n=5)	
ESR(Mean □ SD)		42.78 □ 27.10	65.33 □ 29.23	114.40 □ 34.48	P<0.0001, F=15.624
Sex	Male	13(34.21%)	8(44.44%)	4(80%)	P=0.159,X ² =1.984,df=1
	Female	25(65.79%)	10(55.56%)	1(20%)	
ANA	Positive	14(36.84%)	8(44.44%)	0(0%)	P=0.03,X ² =4.378,df=1
	Negative	24(63.16%)	10(55.56%)	5(100%)	
RF	Positive	2(5.56%)	4(22.22%)	0	P<0.0001,X ² =34.571,df=1
	Negative	34(94.44%)	14(77.78%)	2(100%)	
HLA-B27	Positive	5(13.51%)	0	2(40.00%)	P<0.0001,X ² =34.322,df=1
	Negative	32(86.49%)	17(100%)	3(60.00%)	
Response To Treatment	Positive	30(78.94%)	11(61.11%)	5(100%)	P<0.0001,X ² =15.754,df=1
	Negative	8(21.06%)	7(38.89%)	0	
Early Onset Erosion	Positive	3(7.89%)	4(25.00%)	0	P<0.0001,X ² =33.379,df=1
	Negative	35(92.11%)	12(75.00%)	4(100%)	
Subcutaneous Nodule	Yes	2(5.40%)	1(5.55%)	0	P<0.0001,X ² =48.6,df=1
	No	35(94.60%)	17(94.45%)	5(100%)	
Uveitis	Yes	7(18.42%)	0	0	P<0.0001,x ² =36.213,df=1
	No	31(81.58%)	18(100%)	5(100%)	
Morning Stiffness	Yes	21(55.26%)	9(52.94%)	1(25.00%)	P=0.696,X ² =0.153,df=1
	No	17(44.74%)	8(47.06%)	3(75.00%)	

Table-2. Comparison between males and females regarding to laboratory and clinical features

		Male(n=25)	Female(n=36)	
ESR(Mean <input type="checkbox"/> SD)		73.04 <input type="checkbox"/> 34.17	43.83 <input type="checkbox"/> 30.07	P<0.0001
ANA	Yes	7(28%)	15(41.67%)	P=0.03,X2=4.738,df=1
	No	18(72%)	21(58.33%)	
RF	Yes	2(9.09%)	4(11.76%)	P<0.001,X2=34.571,df=1
	No	20(90.91%)	30(88.24%)	
HLA-B27	Yes	5(21.73%)	2(5.55%)	P<0.0001,X2=34.327,df=1
	No	18(72.27%)	34(94.45%)	
Early Erosion	Yes	4(17.39%)	3(8.57%)	P<0.0001,X2=33.379,df=1
	No	19(82.61%)	32(91.43%)	
Response To Treatment	Yes	21(84.00%)	25(69.45%)	P<0.0001,X2=15.754,df=1
	No	4(16.00%)	11(30.55%)	
Morning Stiffness	Yes	13(56.52%)	18(50.00%)	P=0.696,X2=0.153,df=1
	No	10(43.48%)	18(50.00%)	
Subcutaneous Nodule	Yes	1(4.00%)	2(5.71%)	P<0.0001,X2=48.6,df=1
	No	24(96.00%)	33(94.29%)	
Uveitis	Yes	1(4.00%)	6(16.67%)	P<0.0001,X2=36.213,df=1
	No	24(96.00%)	30(83.33%)	

Table-3: Comparison between ANA positive and ANA negative JRA cases

		ANA Positive(n=22)	ANA Negative(n=39)	
ESR(Mean <input type="checkbox"/> SD)		47.68 <input type="checkbox"/> 27.37	60.05 <input type="checkbox"/> 37.87	P=0.04
HLA-B27	Pos	2(9.09%)	5(13.51%)	P<0.001, X2=34.327,df=1
	Neg	20(90.91%)	32(86.49%)	
Early Erosion	Yes	5(23.80%)	2(5.41%)	P<0.001,X2=33.379,df=1
	No	16(76.20%)	35(94.59%)	
Response to Treatment	Yes	11(50.00%)	35(89.74%)	P<0.001,X2=15.754,df=1
	No	11(50.00%)	4(10.26%)	
Morning Stiffness	Yes	13(61.90%)	18(47.36%)	P=0.69,X2=0.153,df=1
	No	8(38.10%)	20(52.64%)	
Uveitis	Yes	6(27.27%)	1(2.56%)	P<0.0001,X2=36.213,df=1
	No	16(72.73%)	38(97.44%)	
Subcutaneous Nodule	Yes	0	3(7.69%)	P<0.0001,X2=48.6,df=1
	No	21(100%)	36(92.31%)	

DISCUSSION

In the current study we found that response to treatment was higher among ANA negative cases. Shin et al showed that high ANA titer (<1/160) was associated with poor prognosis. Peter Marty et al described a strong association between negative ANA and duration of remission ($p=0.007$).

In the current study, from 61 cases, 22 cases (36.06%) were ANA positive and is similar to Shin et al study.⁸ In a study performed in Greek JIA patients, 41 of 69 cases (59.4%) had ANA positivity and is higher than our study. ANA seropositivity was associated with female sex in Shin et al study.⁸ We found that ANA seropositivity was higher in female sex ($p=0.03$). In another study in Turkish JIA cases, ninety-two girls and 106 boys, totally 148 children were enrolled. Of them 36 (18.2%) were found to be ANA positive. Authors also found that 67.8% of oligoarthritic JIA, 9.75% of polyarthritic JIA, and 7.7% of systemic onset JIA were found to be ANA positive.

From our cases, 62.3% had oligoarthritic JIA, 29.5% had polyarthritic, and 8.2% had systemic onset JIA. In Turkish study, 26.3% of cases were systemic onset JIA.¹¹

In another study in Saudi Arabia, systemic onset disease, is the commonest type. In Kuwait study, polyarthritic (39%) and systemic onset (39%) were the most common form. Quartier et al also reported oligoarthritic as the most common form of disease. Systemic onset disease was found in 4%-44% of cases in different studies. Polyarthritic disease type were found in 18-39% and oligoarthritic type were found in 27-64% in different study. In the Grassi et al study which conducted in Italy on the 309 cases (244 female and 65 male), 193 cases (62.45%) had oligoarthritic, 66 cases (21.35%) had polyarthritic, and 50 cases (16.18%) had systemic onset disease. They found that 20.1% of all cases had uveitis and this is higher than our study. The pattern of disease type is similar to the current study.

Berk et al reviewed 90 cases retrospectively. They found 11 cases (12.2%) with uveitis. Of these cases, seven (63.6%) had oligoarthritic, two (36.4%) had polyarthritic, and one (9.1%) had systemic onset JIA. There was no gender difference in the risk of developing uveitis. They were ANA positive in 7 (63.6%) of 11 cases and confirming that ANA is the strong predictor of developing uveitis in JIA cases.

In the current study, we found that most of the uveitis were seen in ANA positive cases. But all of uveitis cases had oligoarthritic type. In our study, uveitis is significantly higher in female cases ($P<0.0001$, $X^2=36.213$, $df=1$).

Salah S., et al reviewed 196 Egyptian children retrospectively. Male to female ratio was 1/1.09. The mode of onset was oligoarthritic in 41.3%, polyarthritic in 34.7%, and systemic in 24%. Chronic uveitis was found in 5.6% of children. ANA were positive in 21.7% of cases. In the study which carried out in India, 331 children with JRA included. Of these cases, 116 (35.04%) of cases were belonging to oligoarthritic type, 171 (51.68%) cases polyarthritic type, and 44 (13.29%) cases had systemic onset disease.

In Indian study, polyarthritic type is predominant while in our study oligoarthritic is predominant and this may be due to sample size or ethnic difference between two study. JIA has rarely been reported among Black Africans. In 23 cases reported in Nigeria, polyarthritic presentation was the commonest while systemic onset was the least. With studies conducted in different times in different countries, the uveitis incidence in JIA patients was revealed as 2-34%.¹⁸ We found 11.47% as a incidence of uveitis among cases and is similar to other study. Response to treatment was higher among ANA negative and male cases. We found 100% treatment responsiveness among systemic onset and 78.94% in oligoarthritic disease type. RF seropositivity was higher among polyarthritic disease and also female cases. We found morning stiffness in 21 (55.26%) cases with oligoarthritic, 9 (52.94%) of polyarthritic, and 1 case (25%) of systemic onset disease.

In Egyptian study, morning stiffness was found in 53 (65.4%) of oligoarthritic, 45 (66.2%) of polyarthritic, and 30% (63.8%) of systemic onset disease.

In this study, female/male ratio in overall was 1.44:1. In our study, we found female preponderance in all types except systemic onset disease. In Egyptian study, male/female ratio was 1:1.09.¹⁹

In Indian study, there was a male preponderance in three types of disease. Difference in male/female ratio may be due genetic factor among difference country or may be due selection bias in locations of studies.

In conclusion, we found some similarities among our study and other study. Like most of the study, oligoarthritic is the most frequent pattern in Iranian cases. However there is some difference between Saudi Arabia, Kuwait, and India with our results. Some of difference may be the result of ethnic variation. Also, there is several criteria for diagnosis of JRA. Some difference in results may be due to criteria used by different authors.

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