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Original Research Article

Evaluation of serum ferritin and its correlation with disease activity in non-systemic juvenile idiopathic arthritis

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ABSTRACT

Background: Serum ferritin is considered as an acute phase reactant that often increases in presence of an active inflammation. Its status as a disease activity marker is well-established in systemic juvenile idiopathic arthritis (JIA), but underexplored in other categories. The objective of this study was to evaluate the relation of serum ferritin with disease activity in non-systemic categories of JIA
Methods: A prospective analytical study was carried out involving 46 JIA patients (diagnosed and categorized on the basis of ILAR criteria) with high disease activity based on juvenile arthritis disease activity score27 (JADAS27). childhood health assessment questionnaire (CHAQ), erythrocyte sedimentation rate (ESR), serum ferritin, pain VAS (visual analog scale), parent global VAS, JADAS27 were measured at initial visit, six months and one year.
Results: 40 (21 female, 19 male) out of 46 patients completed follow-up of 1 year. Amongst them, 11 patients had systemic arthritis, 10 had oligoarthritis, 11 had RF positive polyarthritis and 8 had RF negative polyarthritis. Their median ages at the initial visit were 7, 6.5, 8 and 7.5 years respectively. Serum ferritin, CRP, ESR, CHAQ score and JADAS decreased over time in all four categories of JIA. Median ESR, ferritin, CHAQ and JADAS27 were higher in systemic JIA compared to other groups in all three visits. Serum ferritin significantly correlated with JADAS27 at all three visits in systemic arthritis; at initial visit in oligoarthritis; at initial visit and 6 months in both RF positive and RF negative polyarthritis.
Conclusions: In patients with systemic JIA, serum ferritin showed significant correlation throughout disease course even when the disease activity was low. But in non-systemic categories of JIA serum ferritin had a significant positive correlation with disease activity only when the disease activity was high.

Keyword: JIA, Disease activity, JADAS, Ferritin

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is arthritis of unknown etiology in children under 16 years of age and persists for at least 6 wks; other known conditions are excluded. It constitutes a heterogeneous group of arthritis in children under 16 years of age.[1] The term 'disease activity' refers to the overall burden of inflammatory disease and this can vary both within and between individuals over time.[2,3] Sustained synovial inflammation may result in irreversible joint destruction leading to deformity and impaired quality of life.[4,5] So, the assessment of the disease activity which represents the continued inflammation is essential for disease monitoring and appropriate therapeutic planning.

A quantitative assessment of disease activity in JIA requires a composite score by combining different individual measures. JADAS is the first such composite measure of disease activity which was developed and validated in 2009.[6] JADAS27 (assessment of 27 joints for active arthritis) is preferred as it is simpler, more feasible and less tedious.[6] C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) is commonly employed acute

phase reactants for monitoring of disease activity. These acute phase reactants have been studied in different categories of JIA where overall changes in their values have been demonstrated during the course of the disease.[7]

Serum ferritin is a well-known marker of acute inflammation.[8] Its role as a disease activity marker has been demonstrated in the context of adult rheumatoid arthritis (RA) and systemic lupus erythematosus.[9,10] In children, particularly in systemic JIA (SJIA) category, serum ferritin showed to be a very good sero-marker of disease activity with a good predictive and prognostic value.[11,12] Increased level of ferritin is one of the characteristic clinical features of macrophage activation syndrome (MAS) which occurs most commonly in sJIA and in its adult equivalent, adult-onset Still's disease.[13]

Although ferritin is appraised as an important inflammatory marker in sJIA, its status has been hardly explored in non-systemic categories of JIAs. The present study was therefore intended to find out the correlation of serum ferritin with disease activity in non-systemic JIAs.

METHODS

This was an analytical observational study with a longitudinal follow up, carried out in the department of pediatrics of I.P.G.M.E and R. and S.S.K.M. hospital, Kolkata, over a period of one and half year from February 2016 through September 2017. The study comprised of JIA patients diagnosed and categorized on the basis of international league of associations for rheumatology (ILAR) criteria.[1] This study included both old and new JIA patients with high disease activity based on JADAS27 score (JADAS27>4.2 in oligoarthritis and>8.5 in polyarthritis).[14,15] Patients with systemic JIA were included following the high disease activity criteria for polyarthritis. All the patients were recruited over a period of 6 months from the indoor and pediatric rheumatology clinic at outpatient department. The patients having any other co-existing chronic inflammatory diseases or having overlap with other rheumatologic diseases were excluded.

The study was undertaken after receiving an ethical clearance from the institutional ethics committee. A written consent was obtained from the parents of all the participants. A detailed history and clinical examination were recorded in a predesigned proforma. All of them had undergone laboratory investigations which included complete hemogram, ESR, and ferritin, urea, creatinine, lipid profile, liver function test, RA factor, anti-nuclear antibody (ANA). Imaging studies included chest X-ray, X-ray and ultra-sonography of affected joints and echocardiography. A particle-enhanced immune-nephelometry using BN II and BN prospect system of auto-analyzer was used for quantitative measurements of ferritin. Treatment was given using the standard therapeutic approach with administration of NSAIDs, corticosteroid, methotrexate and leflunomide. Biologics could not be used due to financial constraints.

Childhood health assessment questionnaire (CHAQ) disability index was used to assess the functional ability.[16] The disability index comprised of 30 items evaluating function in eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities). Scoring for each item was based on a four-point ordinal scale as 0 (without any difficulty), 1 (with some difficulty), 2 (with much difficulty), 3 (unable to do). The global disability index was obtained by calculating the mean of the 8 domains. The score was range from 0 (no disability) to 3 (maximum disability). The parent/child was also asked to complete the 10 cm parent global visual analog scale (VAS) (where 0=very well and 10=very poor) and 10 cm pain VAS (where 0=no pain and 10=maximum pain) provided along with the questionnaire to evaluate the discomfort.

Disease activity was measured by JADAS27 which includes the following parameters:[6.5] a) Physician's global assessment of disease activity (measured on a 10-cm VAS where 0=no activity and 10=maximum activity, b) parent/patient global assessment of well-being (measured on a 10-cm VAS where 0=very well and 10=very poor), c) active joint count (AJC) of 27 joints, d) The erythrocyte sedimentation rate (ESR).

To avoid excessive weight in the overall index, the ESR is converted into a 0-10 normalized scale as follows: [ESR (mm/h)-20]/10. ESR values <20 is allocated a score of 0, and ESR results>120 a score of 10. Score range of JADAS 27 varied from 0-57.

Patients were followed up at regular intervals for a period of 1 year. Measurement of serum ferritin, ESR, CHAQ and JADAS27 score were done at every visit. Data of CHAQ score, pain VAS, parent global VAS, ESR, ferritin and JADAS27 at the initial visit (corresponding to the time of enrolment), 6 months and, 1 year were used for analysis.

Data were presented as frequency (%) or median (inter-quartile range) and compared by Kruskal-Wallis test. Correlation of ESR, and ferritin with disease activity score (JADAS27) were quantified by Spearman's correlation coefficient. $P<0.05$ has been considered as statistically significant. Graph Pad prism version 5 (San Diego, California: GraphPad Software Inc., 2007), SPSS Statistics version 17 (Illinois, Chicago: SPSS Inc., 2008) and statistical version 6 (Tulsa, Oklahoma: Stat Soft Inc., 2001) were used for statistical analysis.

RESULTS

Altogether 46 JIA patients were enrolled after excluding two patients having overlap syndrome with scleroderma. Of those enrolled, one patient with systemic JIA succumbed to MAS and 4 patients were lost to follow-up. One patient was in the category of undifferentiated variety and was excluded from analysis. Of the remaining 40 patients who completed the follow up, 11 (27.5%) had systemic JIA, 10 (25%) had persistent oligoarthritis, 11 (27.5%) had RF positive polyarthritis and 8 (20%) had RF negative polyarthritis. None of the patients could be

categorized as extended oligoarthritis. 21 out of 40 (52.5%) patients were female. Baseline characteristics of the different categories of JIA are shown in Table 1. The median ages of systemic JIA, oligoarthritis, RF positive polyarthritis and RF negative polyarthritis at the initial visit were 7, 6.5, 8 and 7.5 years respectively. Their median disease duration at the time of enrolment in the study was 1, 6, 24, 21 months respectively. All but one systemic JIA and all the oligoarthritis patients were newly diagnosed. None of the patients had uveitis.

Table 1: Baseline characteristics of different categories of JIA at the initial visit.

Parameters	Systemic JIA (n=11)	Oligoarthritis (n=10)	RF positive Polyarthritis (n=11)	RF negative Polyarthritis (n=8)
Female	4 (36)	4 (40)	9 (82)	4 (50)
Age (years)	7 (5-8)	6.5 (6-7.5)	8 (7-10)	7.5 (4.8-9.3)
No. of newly diagnosed cases	10 (91)	10 (100)	4 (36)	3 (38)
Duration of disease (months)	1 (0.5-1)	6 (6-6)	24 (6-36)	21 (6-25)
No. of RF positive patients	4 (3.64)	1 (10)	11 (100)	0 (0)
RF titer (IU/mL)	10.3 (9.3-192)	9.8 (9.5-10.1)	232 (123-301)	8.3 (7.9-9.9)
No. of ANA positive patients	0 (0)	7 (70)	0 (0)	2 (25)

Values are frequency (%) or median (inter-quartile range); RF, rheumatoid factor; ANA, anti- nuclear antibody.

Table 2: Comparison of disease activity parameters in different categories of JIA patients.

Parameters	Visits	Systemic JIA (n=11)	Oligoarthritis (n=10)	RF positive Polyarthritis (n=11)	RF negative polyarthritis (n=8)
CHAQ score	Initial	2.75 (2.50-2.80)	0.94 (0.75-1)	1.37 (1.13-1.87)	1.56 (1.39-1.87)
	6 months	1.50 (1.38-1.88)	0.50 (0.38-0.63)	0.88 (0.75-1)	0.80 (0.69-1)
	1 year	1 (0.75-1.25)	0.31 (0.25-0.40)	0.50 (0.38-0.63)	0.46 (0.40-0.69)
Pain VAS (cm)	Initial	8.2 (7.6-8.5)	4.3 (3.8-4.6)	5.3 (3.7-6.1)	5.1 (4.4-5.7)
	6 months	4.9 (4.2-5.3)	2.0 (1.5-2.1)	2.9 (2.3-3.3)	2.9 (2.7-3.2)
	1 year	2.6 (1.9-3.8)	1.2 (1.1-1.6)	1.7 (1.2-1.9)	1.7 (1.5-2.1)
Parent global VAS (cm)	Initial	8.1 (7.2-8.2)	4.1 (3.3-4.3)	6.2 (3.6-6.3)	4.9 (4.5-6.1)
	6 months	4.2 (4.0-5.1)	1.9 (1.1-3.1)	3.2 (2.3-4.1)	3.1 (2.9-3.5)
	1 year	2.1 (2.1-3.2)	1.1 (1.1-1.2)	2.0 (1.1-2.3)	1.9 (1.8-2.3)
ESR (mm/hr)	Initial	120 (114-120)	56 (42-68)	79 (74-97)	65 (57-83)
	6 months	72 (62-86)	32 (27-45)	50 (37-62)	50 (38-56)
	1 year	40 (29-47)	25 (20-30)	32 (24-34)	33 (30-34)
Ferritin (ng/ml)	Initial	4791 (4190-5785)	146 (95.8-188)	267 (198-302)	127 (105.5-197.5)
	6 months	640 (509-716)*	98.7 (97-129)	160 (124-198)*	119 (93.3-132.5)
	1 year	249 (217-299)***	89.4 (84.6-109)**	119 (112-157.8)***	105.1 (94.2-125)
JADAS27	Initial	29 (28-30.4)	12.7 (10.7-15.7)	22.7 (14.4-24.9)	21.8 (19.4-26.3)
	6 months	18 (14.2-19)*	5.6 (4.2-9.4)	13.5 (8.6-15.1)	13 (11.3-16.1)
	1 year	8.3 (7.4-9.8)***	2.5 (2-3)***	6.2 (5.2-8.4)***	7.6 (6.7-8.2)***

Values are med Values are median (inter-quartile range), * $p<0.05$ in comparison to initial value, ** $p<0.01$ in comparison to initial value *** $p<0.001$ in comparison to initial value, Ferritin and JADAS27 at initial visit were compared with those at 6 months and 1 year by Kruskal-Wallis test followed by Dunn's multiple comparison test.

CHAQ score, pain VAS, parent global VAS, ESR, ferritin and JADAS27 at the initial visit, 6 months and 1 year follow-up have been shown in Table 2. All the parameters were higher in systemic JIA in all three visits compared to others. The values of all the parameters were highest at the initial visit that decreased with time and were lowest at the end of 1 year of follow-up in all four categories of JIA. There was significant drop in ferritin level in systemic JIA and RF positive polyarthritis at 6 months and in oligoarthritis at 1 year. In case of RF negative polyarthritis, ferritin did not decrease significantly even at 1 year. Significant decrease in disease activity was observed at 6 months in systemic JIA. However, JADAS 27 score decreased significantly only at the end of 1 year in oligoarthritis (median score 12.7 at initial visit vs 2.5 at 1 year), RF positive polyarthritis (22.7 vs 6.2) and RF negative polyarthritis (21.8 vs 7.6). Mean with standard deviation of ESR, ferritin and JADAS27 of non-systemic JIA at different visits has been shown in Figure 1.

Correlation of JADAS27 with ESR and ferritin in different categories at different visits has been shown in Table 3. The table shows that serum ferritin significantly and positively correlated with JADAS27 in systemic JIA throughout the one-year follow-up period. In case of oligoarthritis patients, statistically significant positive correlation of serum ferritin with disease activity score was found only at the initial visit, and not at 6 months (Figure 2). Ferritin, as shown in the table, had significant

correlation with disease activity score in RF positive polyarthritis and RF negative polyarthritis at the initial visit and also at 6 months follow-up (Figure 2). Additionally, it has been found that ESR correlated significantly with JADAS27 only at the initial visit in RF positive category.

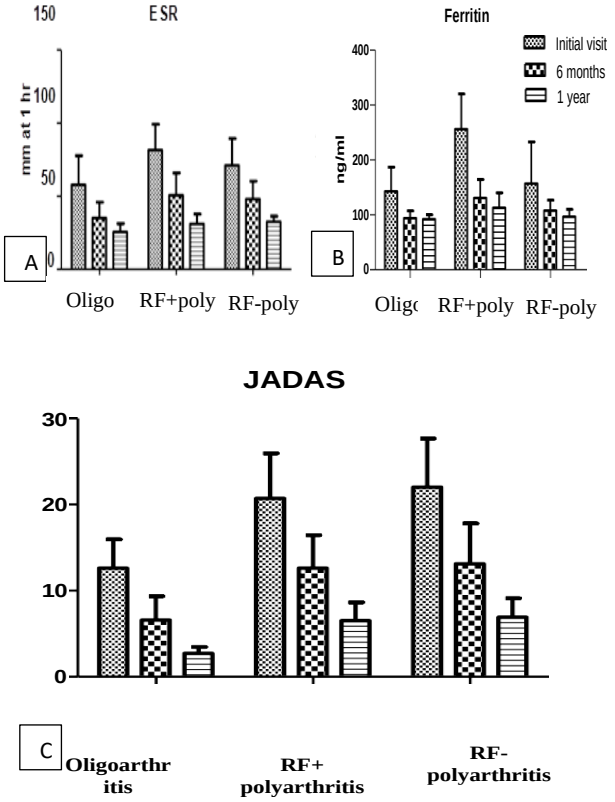

Figure 1: Mean ESR, ferritin and JADAS27 in different categories of non-systemic JIA at initial visit, 6 months and 1 year; the error bars indicate standard deviations.

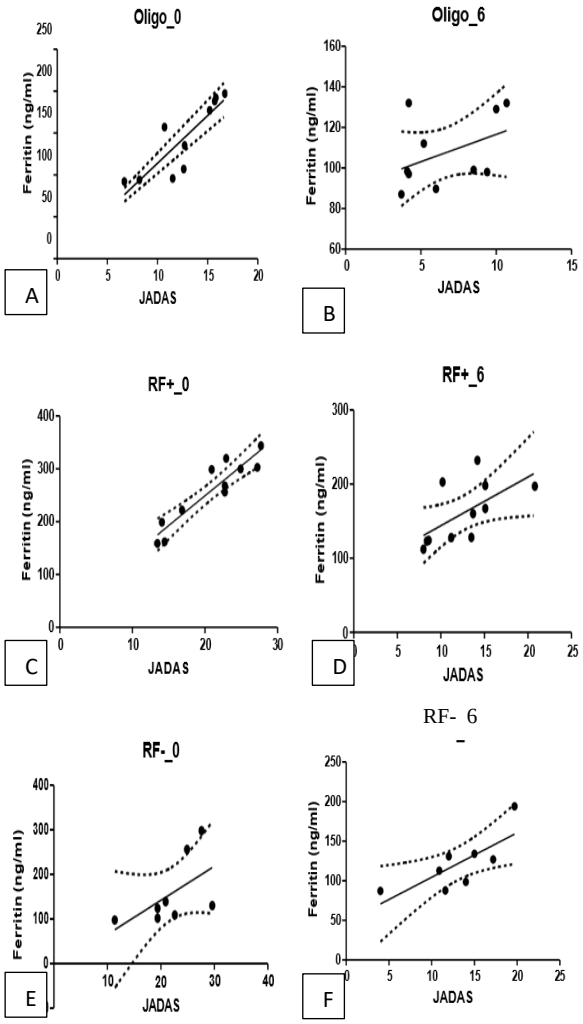

Figure 2: Scatter plots with linear regression of ferritin with JADAS27 at initial visit and 6 months post- treatment in oligoarthritis, RF positive polyarthritis and RF negative polyarthritis; the solid lines are the best-fit lines; the dashed lines are 95% confidence bands.

Table 3: Correlation of JADAS27 with inflammatory markers in different categories of JIA at different visits.

Visits			ESR	Ferritin
Systemic JIA	Initial	Spearman's rho	0.128	0.917
		P value	0.709	<0.0001
	6 months	Spearman's rho	0.630	0.964
		P value	0.038	<0.0001
	1 year	Spearman's rho	0.644	0.773
		P value	0.033	0.005
Oligoarthritis	Initial	Spearman's rho	0.855	0.927
		P value	0.002	0.0001
	6 months	Spearman's rho	0.780	0.491
		P value	0.008	0.150
	1 year	Spearman's rho	0.987	0.577
		P value	<0.0001	0.081
RF positive polyarthritis	Initial	Spearman's rho	0.661	0.934
		P value	0.027	<0.0001

Continued.

Visits			ESR	Ferritin
	6 months	Spearman's rho	0.543	0.711
		P value	0.084	0.014
	1 year	Spearman's rho	0.390	0.498
		P value	0.236	0.119
RF negative polyarthritis	Initial	Spearman's rho	0.873	0.743
		P value	0.005	0.035
	6 months	Spearman's rho	0.905	0.786
		P value	0.002	0.021
	1 year	Spearman's rho	0.659	0.238
		P value	0.076	0.570

DISCUSSION

Our study revealed that there was significant decrease in disease activity in all categories of non-systemic JIA at the end of 1 year. However, the decrease in ferritin level was not that uniform. A significant drop in ferritin level was observed in RF positive polyarthritis at 6 months and in oligoarthritis at 1 year follow up, whereas ferritin did not decrease significantly even at 1 year in subjects with RF negative polyarthritis. However, a strong correlation of ferritin with JADAS27 was detected at initial visit and at 6 months in both RF positive and RF negative polyarthritis when disease activity was high. In oligoarthritis subjects, a significant positive correlation was found only at the initial presentation. At 1 year follow up, when the disease activity was low following treatment, no significant correlation was found in non-systemic subjects.

Serum ferritin is an iron storage protein. Although it is not synthesised in the serum, it is present in high titre during the acute phase of inflammation and is a marker of cellular damage.[8] A leakage from the damaged cell or direct cytokine mediated activation could be responsible for high ferritin level.[8,17] There is an argument in recent times whether ferritin could be considered as a better marker of inflammation than of iron status especially in countries where inflammatory diseases are highly prevalent.[8]

In adult populations with arthritis and other inflammatory disorders, serum ferritin is a well- known inflammatory marker as reported in several literatures. Elevated levels of glycosylated and basic ferritin were found in 89% of patients with adult-onset Still's disease.[17] In another study, the mean ferritin was higher in RA patients with active disease compared to inactive disease (utilizing the DAS28 score).[18] Serum levels of ferritin during the more active stage of SLE exceeded those of RA patients and patients at less active stages of SLE.[19,20]

In children, however, serum ferritin has established its status as a disease activity marker only in systemic JIA. This particular category of patients develops MAS more frequently and ferritin is considered as a reliable biomarker.[11-13] A good correlation between ferritin level and therapeutic response was demonstrated in the literature. An elevated ferritin level had been shown to predict the development of MAS and a rapid decline in ferritin could designate a favorable prognosis.[21,22] Reports on serum ferritin level in non-systemic JIA are scarce. In an earlier study, serum ferritin was found to be a reliable marker of disease activity in juvenile chronic polyarthritis.[23]

Small sample size of individual JIA categories is a limitation of this study. According to the institutional policy, only children up to the age of 12 yrs are registered in the pediatric department. So, patients above 12 yrs were not evaluated. All children belonged to same South Asian ethnicity, so conclusion may not be held true universally. There was no case of enthesitis-related arthritis or psoriatic arthritis. Moreover, among the oligoarthritis subjects, none had extended oligoarthritis. Hence ferritin could not be evaluated in these categories.

CONCLUSION

In conclusion, serum ferritin showed a significant correlation with JADAS27 in oligoarthritis and polyarthritis categories at the time of inclusion, when disease activity was high. Both the categories of polyarthritis patients, in addition, showed a significant correlation even at 6 months follow up when disease activity was still high. Further studies incorporating a large number of samples with a longer duration of follow-up are required to consolidate the status of ferritin as a seromarker in non-systemic JIAs.

Our study revealed that there was significant drop in ferritin level in RF positive polyarthritis at six months and in oligoarthritis at 1 year follow up. Whereas, ferritin did not decrease significantly even at 1 year in subjects with RF negative polyarthritis. However, a strong correlation of ferritin with JADAS27 was detected at initial visit and at six months in both RF positive and RF negative polyarthritis when disease activity was high. In oligoarthritis subjects, a significant positive correlation was found only at the initial presentation. At one year follow up, when the disease activity was low following treatment, no significant correlation was found in non-systemic subjects.

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