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Original Research Article

Profile of anemia in children with juvenile idiopathic arthritis

Debarghya Pan[1], Madhumita Nandi[2]*, Moumita Samanta[3], Nikhil Gupta[4]

[1]Department of Pediatrics, Calcutta National National Medical College, Kolkata, West Bengal, India
[2]Department of Pediatrics, North Bengal Medical College, Darjeeling, West Bengal, India
[3]Department of Pediatrics, Medical College, Kolkata, West Bengal, India
[4]North Bengal Medical College, Darjeeling, West Bengal, India

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***Correspondence:**
Dr. Madhumita Nandi,
E-mail: madhumitabanik@rediffmail.com

ABSTRACT

Background: Anemia is one of the commonest extra-articular manifestations or complications associated with juvenile idiopathic arthritis (JIA) and is generally seen to corelate with disease-duration and disease-activity. Aim of the study was to find out the prevalence of anemia, its etiological spectrum and severity in children suffering from JIA, to determine its correlation with disease-activity and disease-duration and assess the change in the status of anemia after initiating cause- specific treatment in addition to disease-specific treatment in a follow-up period of 3 months.
Methods: This prospective longitudinal observational study was conducted in a tertiary care teaching hospital from July to December 2022. Patients of JIA were recruited through purposive sampling stratified by disease activity based on juvenile arthritis disease activity score (JADAS) 27 score and anemia categorized by World Health Organization (WHO) criteria.
Results: A total of 64 children were included in the final analysis. Mean age of patients was 8.19 years (SD 2.34 years), male: female ratio being 1.2:1. 78.12% were anemic, with 59.37% being moderately anemic. Overall, anemia-of-chronic-disease (ACD) was the most (48%) prevalent type of anemia, followed by iron-deficiency-anemia (IDA) at 28%, followed by a combination of both IDA and ACD (12%). Remaining 12% was attributed to other causes of anemia. Mean-hemoglobin at 1st visit was found to decrease with increase in disease duration. Significant moderate linear negative correlation was found ($r=-0.54$) ($p<0.001$) between mean-hemoglobin-at-1st-visit and mean-disease-activity-at-1st-visit. Significant rise in hemoglobin level after initiation of cause-specific treatment with disease-specific treatment was also observed in this study.
Conclusions: Anemia associated with pediatric rheumatological conditions has significant negative impact on the disease process. Prompt diagnosis of anemia, denoting its type and severity, and thereby treating anemia alongside disease-specific treatment, significantly improves the patient outcome.

Keywords: Anemia, Juvenile idiopathic arthritis, Treatment

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is one of the commonest chronic rheumatological disease of childhood.[1] Anemia is one of the common accompaniments of this condition which is often multifactorial in origin. The disease process itself, complications like macrophage activation syndrome and nutritional deficiencies may all contribute to pathogenesis of anemia in such children. It is important that such children are screened and managed in time to avoid the short- and long-term complications of low hemoglobin including its' impact on overall quality of life and physical growth.

Given the possible magnitude of the problem, there is really a dearth of studies on this important aspect of JIA especially from the eastern part of this country. Hence this study is an attempt to delineate the causes, severity and

possible remedial measures of anemia in children suffering from JIA.

Aims and objectives

Aims and objectives were to find out the prevalence of anemia, its etiological spectrum and severity in children with JIA attending a tertiary care teaching hospital in Eastern India, determine its correlation with disease activity and disease duration and assess the change in the status of anemia after initiating cause- specific treatment in addition to disease-specific treatment on follow-up after 3 months.

METHODS

Study setting and participant selection

This single-centre, prospective longitudinal, observational study, was performed at a tertiary care teaching hospital of eastern India from July to December 2022. Children between 1 month and 12 years of age fulfilling the International League of Association for Rheumatology (ILAR) classification criteria for JIA were initially screened for inclusion.[2,3] The participants were recruited through a purposive sampling technique, which was stratified by the current status of their disease activity. Critically ill and those with known comorbidities, were excluded.

Approval for the study was obtained from Institutional Ethics Committee (IEC/NBMC/2021-22/25) and written informed consent was obtained from each participant or their guardian as applicable.

Data collection

The epidemiological and clinical background information of each participant was entered in a predesigned pretested proforma. To assess the disease activity, juvenile arthritis disease activity score 27 (JADAS 27), which included a list of 27 pre-selected joints for evaluation, was utilized. JADAS27 comprises following four measures: physician's global assessment of disease activity, [measured on a 0–10 visual analogue scale (VAS) where 0 indicated no activity and 10 meant for maximum activity]; parent global assessment of well-being, (measured on 0–10 VAS, where 0 equivalent to very well and 10 equivalent to very poor); erythrocyte sedimentation rate (ESR) in millimetres per hour (normalized to a 0–10 scale using the formula of {[(ESR mm/hour) – 20]/10}, and; a count of joints with active disease. The list of joints included cervical spine, elbows, wrists, metacarpophalangeal joints (from first to third), proximal interphalangeal joints, hips, knees, and ankles for the purpose of assessing disease affliction. JADAS 27 score was calculated as a linear sum of the four components yielding a global score of 0–57. The cut-off scores for inactive disease, low disease activity, moderate disease activity, and high disease activity were set to be ≤1, 1.1–2, 2.1–4.2, and >4.2 in oligoarthritis and ≤1, 1.1–3.8, 3.9–8.5, and >8.5 in polyarthritis, respectively.[4]

Clinical and laboratory data were filled up on inclusion at presentation and at 3 months in a predesigned and pretested proforma. Hemoglobin levels, mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), was carried out via automated analyzer (5-Part Sysmex XN330) and corroborated with microscopic examination of peripheral blood smears. Serum ferritin levels were estimated using chemiluminescent immunoassay (CLIA). Anemia was classified into 4 categories as: iron deficiency anemia (IDA), anemia of chronic disease (ACD), both IDA and ACD, and other types such as anemia of blood loss, and hemolytic anemia.[5,6] Severity of anemia was classified as: no anemia, mild, moderate and severe as per WHO classification for each age group.[7,8]

Statistical analysis

All the information collected was compiled using Microsoft excel 2016 software. Obtained data were summarized with routine descriptive statistics to find the mean and standard deviations (SDs) for the numerical variables and counts and percentages for the categorical variables. Statistical analysis was performed with the help of statistical package for the social sciences (SPSS) version 25.0. Student's t-test was applied to compare different numerical variables, when one of the variables was categorical. One-way analysis of variance (ANOVA) followed by post hoc Tukey's B test was performed where more than two or more continuous variables were compared simultaneously. Test of proportion was used to find the standard normal deviate (*Z*) to compare the categorical variables, and chi-square test was performed to find their association in between. A p value of <0.05 was taken to be statistically significant.

RESULTS

Out of a total of 74 patients initially assessed for eligibility, 4 were excluded as they met one or more exclusion criteria as mentioned above. So, the initial sample size (n) was 70. As 6 patients were lost to follow up, data of 64 patients could be compiled and analysed at the end of 3 months (Figure 1). In this cohort, mean (SD) age of presentation was 8.19 (2.34) years with a male: female ratio of 1.1:1 (34:30). 31 (48.43%) were of oligoarticular variety, 23 (35.93%) were of polyarticular variety, 10 (15.62%) had JIA. None were from psoriatic, ERA and unclassified subtypes (Table 1).

Overall anemia was present among 78.12% of the children with majority i.e., 59.37% having moderate anemia, 12.5% being severely anemic and only 6.25% being mildly anemic. ACD was the most common (48%) type of anemia, followed by IDA at 28%, followed by a combination of both IDA and ACD accounting for 12%. Remaining 12% was attributed to others causes of anemia

[like autoimmune hemolytic anemia (AIHA), and anemia of chronic blood loss] (Tables 1-3).

Table 1: Patient characteristics at presentation and at 3 months of follow up.

Clinical profile	At presentation (n=70), N (%)	At 3 months follow up (n=64) N (%)
Gender		
Male	36 (51.43)	34 (53.13)
Female	34 (48.57)	30 (46.87)
JIA category		
Oligo-articular JIA	31 (44.28)	31 (48.44)
Polyarticular JIA	25 (35.72)	23 (35.94)
Systemic onset JIA	14 (20)	10 (15.62)
JADAS 27		
Low	11 (15.71)	14 (21.88)
Moderate	15 (21.42)	21 (32.81)
High	44 (62.85)	29 (45.31)
Anthropometry		
Stunting	50 (71.42)	45 (70.31)
Wasting	18 (25.71)	17 (26.56)
Underweight	32 (45.71)	32 (50)
Anemia		
No	16 (22.85)	14 (21.87)
Mild	4 (5.71)	6 (9.37)
Moderate	40 (57.14)	42 (65.62)
Severe	10 (14.28)	2 (3.12)

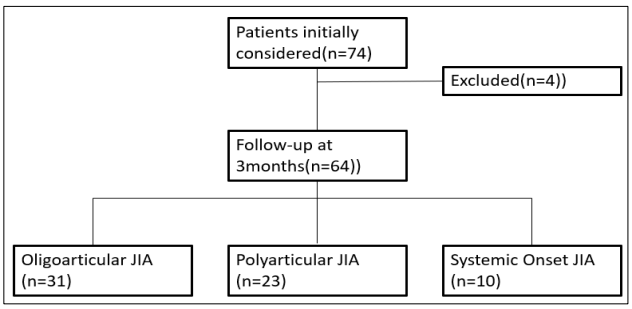

Figure 1: Consort (study flow).

Mean disease activity (SD) was significantly more in anemic children with JIA 26.50 (6.9) than non-anemic 20.13 (2.8) (p<0.01). A moderate negative linear correlation (r=-0.54), with Pearson correlation was observed between mean disease activity (1st visit) of the patients and the hemoglobin levels, the association being statistically significant (p<0.001) (Figure 2).

The current study also showed that with children receiving cause specific and disease specific treatment the mean (SD) hemoglobin level overall at first and at 3 month follow-up visit was 9.76 gm/dl (2.26) and 10.39 g/dl (1.62), respectively, this increase being statistically significant (p<0.001) (Figure 2) with a significant decrease in mean disease activity score at follow up visit, 15.89 (7.2) as compared to 1st visit 24.89 (6.8) (p<0.001) (Figure 3). Group specific analysis revealed that in children with JIA and IDA the rise of mean (SD) Hb (gm/dl) in 1st and follow up visit was 8.89 (2.3) and 9.75 (1.3) respectively. Similar observations in ACD, both IDA and ACD and other causes were 8.85 (2.2) versus 9.79 (1.4), 9.36 (2.3) versus 9.85 (1.4), 8.91 (2.4) versus 9.65 (1.5) respectively. With follow up there was significant (p<0.05) improvement of disease activity score in JIA patients with IDA [22.14 (7.7) versus 11.85 (9.1)], ACD [24.77 (6.5) versus 16.75 (5.2)] and both IDA and ACD [25.49 (1.2) versus 15.82 (2.1)]. Significant reduction of disease activity was not found in anemia due to other cause group [31.6 (5.1) versus 23.5 (10.6); p=0.12].

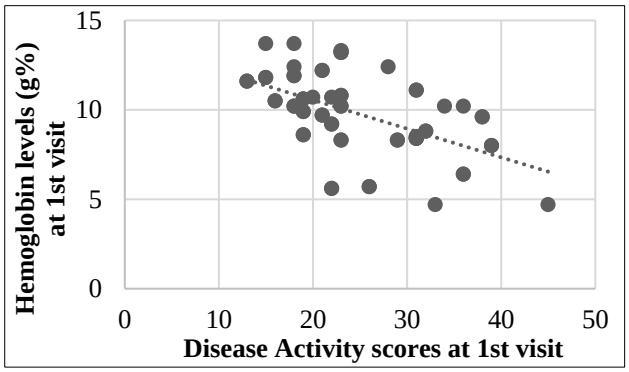

Figure 2: Correlation between hemoglobin levels (g%) and disease activity scores at 1st visit.

Mean Hb (gm/dl) at 1st and follow up visit for patients with disease duration <2 years, 2-4 years and >4 years were respectively 10.45 and 10.72, 9.55 and 10.66, 10.21 and 11.53, the increase being statistically significant for all 3 groups (p<0.001). A statistically significant mild linear negative correlation (r=-0.23) with Pearson co-relation was also observed between hemoglobin levels of patients and mean duration of diseases (p=0.032) (Figure 4).

Table 2: Distribution and association of severity of anemia according to disease category.

Anemia (1st visit)	JIA subtype (%)				P value
	Oligoarticular	Polyarticular	SJIA	Total	
None	5	5	4	14	
Mild	0	4	0	4	
Moderate	22	14	2	38 (59.37)	0.04*
Severe	4	0	4	8	
Total (n=64)	31 (48.43)	23 (35.93)	10 (15.62)	64	

*Chi-square test

Table 3: Distribution of type of anemia according to disease group.

Disease group	Type of anemia (%)				P value
	IDA	ACD	Both	Others	
Oligoarticular	8	12	2	4	0.013*
Polyarticular	4	10	4	0	
SJIA	2	2	0	2	
Total (n=64)	14 (28)	24 (48)	6 (12)	6 (12)	

*Chi-square test

Table 4: Showing anthropometric parameters among anemic and non-anemic children.

Anthropometric parameters	Anemic patients (%)	Non-anemic patients (%)	P value
Stunted	37 (74)	8 (57)	0.23*
Not stunted	13 (26)	6 (43)	
Underweight	27 (54)	5 (36)	1.2*
Not underweight	23 (46)	9 (64)	
Wasted	15 (30)	2 (17)	0.67*
Not wasted	35(70%)	12(83%)	

*Chi-square test

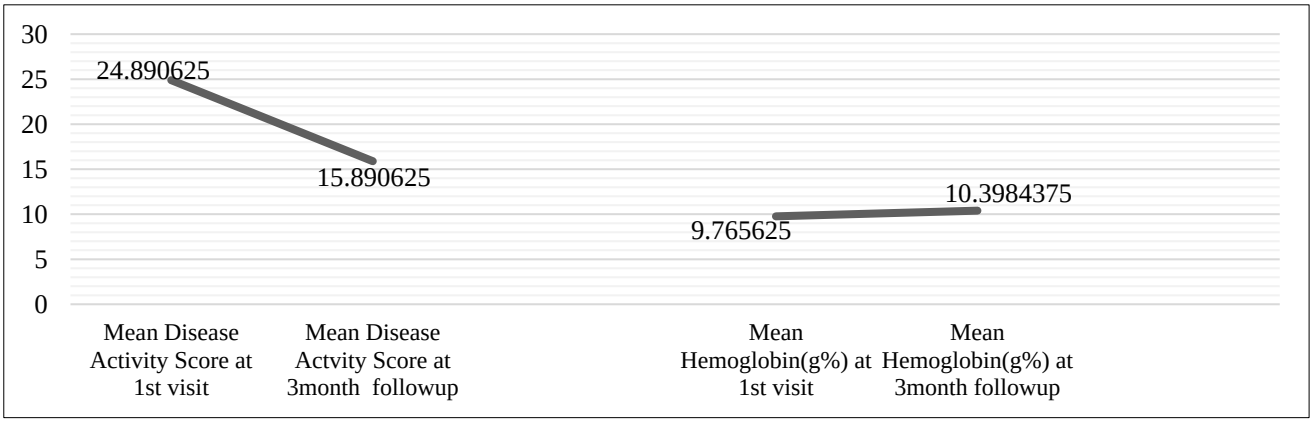

Figure 3: Mean hemoglobin levels (g%) and mean disease activity scores at 1st visit and at 3 months follow up.

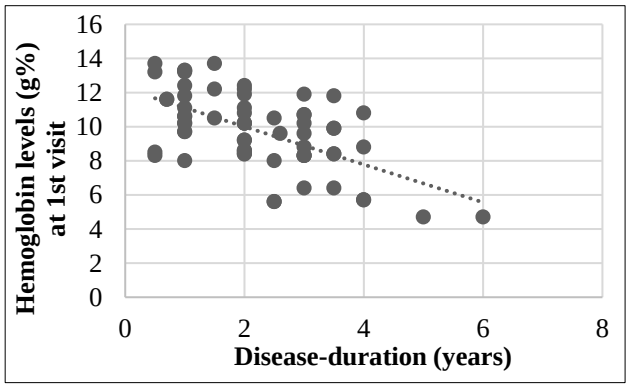

Figure 4: Correlation between hemoglobin levels (g%) at 1st visit and disease-duration (years).

As regards the overall growth characteristics of this cohort, the anemic children, 74% had stunting, 54% were underweight, 30% had wasting as compared to the non-anemic children, whereas, 57% were stunted 34% were underweight, while 16.6% had wasting, though the difference was not statistically significant (Table 4). Proportions of anemia were more among shunted and severely underweight male children, in less than 4-year age group and those with disease duration of 2-4 years.

DISCUSSION

Table 5 compares the important outcomes of the present study with previous published studies on this issue. Out of a total of 64 pediatric patients included in the study, we observed that mean (SD) age of presentation of JIA in children was 8.19 (2.34) years. These findings were found to corroborate with findings of a study done on Thai patients with JIA by Buaboonnam et al, where median age of JIA patients was found to be 8.1 years.[9] Riaaz et al from Bangladesh concurred similar findings, with median age group of JIA patients in their study being reported as 9.36 years (SD-3.51).[11] Singh et al from Chandigarh, India mentioned the mean age of presentation of pauciarticular and polyarticular JIA patients were 7.4 years and 7.0 years respectively.[10]

Table 5: Comparison of present study with relevant previous studies.

S. no.	Author/place/ year	Study subject	Sample size	Age group (years)	Results
1	Koerper et al/USA/1978[13]	Children with JRA	51	<16	Patients with JIA have anemia attributable to the chronic disease, to iron deficiency, or to a combination of the two. 11/15 anemic patients with JIA corrected their anemia after 3 to 6 months of iron therapy.
2	Singh et al/India/1999[10]	JRA patients	74	<16	Anemia - seen in 75% of the patients.
3	Buaboonnam et al/Thailand/ 2017[9]	JIA patients	55	<16	Anemia of inflammation - present in 87% patients. Other causes of anemia: coexisting anemia of inflammation and IDA, and coombs-positive hemolytic anemia.
4	Riaz et al/Bangladesh/ 2020[11]	JIA patients	80	<16	41% percent of JIA patients had moderate anemia. Significant negative correlation, between Hb concentration and disease duration. Significant relationship of disease activity with anemia in JIA patients.
5	Present study/ India/2022	Pediatric patients with JIA	64	<12	Anemia seen-78.12%, moderate anemia-59.37%, M/C type of anemia- ACD, mean Hb levels decreased significantly with disease duration, significant moderate linear negative correlation between Hb levels (g%) and mean diseases activity at 1st visit. Significant rise in Hb levels after 3 months of cause-specific treatment.

The sex distribution of the patients revealed a slight male preponderance with approximately 53% being males and 47% being females. Singh et al in their study showed male to female ratio among JIA patients in Chandigarh, India to be 1.8:1.[10] Same was reported in a study by Seth et al in India and by Riaaz et al from Bangladesh, with a significantly high male predominance.[11,12] However many western literature, show a slight female preponderance amongst JIA patients, has also been reported by Buaboonnam et al in their study on Thai patients with JIA, that 61% of their subjects were females and only 39% being males which contradicted to our study.[9] Yet, the works by most Indian authors suggest a male preponderance in contrast to females. While it is possible that male predisposition may represent a natural characteristic of JIA in India, the fact that boys are cared and brought to medical attention earlier than girls in our country may also contribute largely to this discordance with the western data.

As per the current study, overall anemia was present among 78.12% of the children with majority (59.37%) having moderate anemia, 12.5% being severely anemic and only 6.25% being mildly anemic. ACD was the most common (48%) type of anemia, followed by IDA at 28%, followed by a combination of both IDA and ACD accounting for 12%. Remaining 12% was attributed to others causes of anemia (like AIHA, and anemia of chronic blood loss). These findings are also in concordance with the observations made by Buaboonnam in Thai patients with JIA, as in Anemia being the most common hematological manifestation seen in almost 83.6% cases, with anemia of chronic inflammation being found in 86.9% of the patients with anemia, those made by Riaaz et al in Bangladeshi patients with JIA, with anemia being present in 91.25% of their study subjects, majority (41%) of them having moderate anemia, 31.5% and 27.4% having mild and severe anemia, with anemia of chronic disease being the commonest cause and often being indistinguishable from iron deficiency anemia.[9,11] A study done by Koerper on American children, showed that 11 out of 15 anemic patients of JIA raised their mean hemoglobin by 1.0 g/dl with 3-6 months of oral iron therapy, indicating the anemia associated with JIA is at least partly due to correctible iron deficiency.[13] This finding was similar to that of our study where we found improvement of Hb from 9.76 gm/dl to 10.39 gm/dl over 3 months with therapy.

Longer disease duration was associated with significantly lower Hb levels at first visit ($r=-0.23$; $p<0.032$). Similar observations were made by Riaaz et al as well where a significant negative correlation ($r=-0.290$, $p=0.009$) was found between Hb concentration and diseases duration of patients with JIA.[11]

Children with higher mean disease activity (1st visit) had significantly lower Hb levels ($r=-0.54$, $p<0.001$). Riaaz et al in their study on Bangladeshi JIA patients, also observed a similar statistically significant relationship between the presence of anemia and mean diseases activity at presentation.[11] Buaboonam et al in their study too found that Hb levels were negatively correlated with JIA disease activity in Thai children.[9]

Although this study highlights some of the important aspects of anemia in children with JIA, small sample size, short duration of follow up, absence of a control arm, lack of advanced diagnostic facilities to pinpoint the exact

pathogenesis of anemia in such children were some of the limitations. Further long term, larger multicentric studies are called for to arrive at more robust results related to incidence and consequences of anemia in children with JIA.

CONCLUSION

Anemia forms a significant burden in chronic rheumatological disorders in children and usually with increase in disease duration, anemia burden also increases. Cause specific treatment of anemia along with disease specific treatment significantly improves outcome. However, modern literature still lacks fixed and validated guidelines with respect to managing anemia in pediatric rheumatological conditions. Further studies with larger sample sizes need to be carried out on this topic and a definitive guideline on the management of anemia in these children must be laid down at the earliest to reduce the morbidity and mortality associated with these conditions.

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