HEMATOLOGIC INVOLVEMENT IN THAI PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

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Abstract. Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children. Hematologic involvement among patients with JIA is prevalent and varied, ranging from anemia to macrophage activation syndrome (MAS). The aim of this study was to characterize hematologic manifestations and to identify a relationship between anemia of inflammation at the time of diagnosis and disease activity and parameters in Thai patients with JIA. Medical records of 55 children with JIA were reviewed. Disease activity was assessed using the Juvenile Arthritis Disease Activity Score 71 (JADAS-71). The most common hematologic manifestation was anemia (83.6%). Anemia of inflammation was found in 86.9% of JIA patients with anemia. Patients with systemic JIA had significantly more leukocytosis (p<0.001), neutrophilia (p<0.001), MAS (p=0.031), and severe anemia requiring blood transfusion (p=0.008) than patients with non-systemic JIA. Anemia of inflammation at the time of JIA diagnosis was significantly associated with higher erythrocyte sedimentation rate (ESR) (p<0.001) and C reactive protein (CRP) concentration (p<0.001). Hemoglobin level was negatively correlated with arthritis joint count (r=-0.171), physician global assessment of disease activity (r=-0.084), patient/parent global assessment of well-being (r=-0.085), JADAS-71 (r=-0.351), ESR (r=-0.555), and CRP concentration (r=-0.536). Anemia of inflammation was common in Thai patients with JIA. Children with systemic JIA had more severe hematologic involvements than those with non-systemic JIA. Hemoglobin level was negatively correlated with JIA disease parameters, most of which were acute-phase reactants. Early and aggressive treatment of JIA may lessen anemia in JIA patients.

Keywords: juvenile idiopathic arthritis, anemia, Juvenile Arthritis Disease Activity Score, hemoglobin, children

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children. It is characterized by chronic arthritis that begins before 16 years of age that persists for at least 6 weeks. JIA is currently classified into 7 subtypes based on clinical features and the number of joints involved (Petty *et al*, 2004). Children with JIA may develop complications of chronic arthritis, including leg length discrepancy, muscle atrophy, and joint deformities (de Oliveira Sato *et al*, 2011; Magni-Manzoni *et al*, 2008). Well-known extra-articular complications of JIA include uveitis, growth disturbance, and osteopenia (Bechtold and Simon, 2014; Sen *et al*, 2015). More importantly, hematologic involvement in

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JIA is a pivotal extra-articular complication that can range from anemia, the least severe complication, to macrophage activation syndrome (MAS), a potentially fatal condition (Minoia *et al*, 2014). However, studies in and data relating to hematologic involvement in patients with JIA are scarce. Previous studies have reported that anemia, particularly anemia of inflammation, is the most common hematologic finding; however, the association between anemia and disease-related factors, such as active joint count and disease activity index, has not been well elucidated (Harvey *et al*, 1987; Kirel *et al*, 1996). Juvenile Arthritis Disease Activity Score 71 (JADAS-71) is widely used in current clinical practice (Consolaro *et al*, 2009). In addition, the relationship between severity of anemia of inflammation and disease activity scoring by metrics such as JADAS-71 in patients with JIA has not been investigated.

The incidence of JIA in Southeast Asian countries (including Thailand) are different from those reported in Western countries, with systemic JIA being the most prevalent type among Asians and oligoarthritis being the most common type among Westerners (Fujikawa and Okuni, 1997; Weiss and Ilowite, 2005; Vilaiyuk *et al*, 2015). Additionally, pre-existing anemia due to hemoglobinopathies and iron deficiency anemia (IDA) was shown to be more common in Thailand and other developing countries than in the West (Viprakasit *et al*, 2013). As a result, making the correct diagnosis of anemia in these JIA patient populations is more challenging. Moreover and given that both IDA and thalassemia are very common among Thai populations, it is even more difficult to correctly diagnose anemia, since these Thai patients may have preexisting IDA and thalassemia before developing JIA. To the best of our knowledge, no previous studies have investigated anemia in JIA patients that come from a region with a high prevalence of inherited anemia.

The objective of this study was to describe common hematologic manifestations and to investigate the relationship between anemia of inflammation at the time of diagnosis and disease activity and parameters in Thai children with JIA.

MATERIALS AND METHODS

We retrospectively analyzed our patient database at the Division of Rheumatology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University and identified 55 patients that were diagnosed with JIA during the July 2011 to June 2015 study period. Disease subtypes in all patients were determined according to International League of Associations for Rheumatology criteria (Petty *et al*, 2004). We collected demographic and clinical information, including gender, ethnicity, age at disease onset, age at diagnosis, and JIA subtype. Disease activity was determined using the JADAS-71 (Consolaro *et al*, 2009) assessment tool. The JADAS-71 includes a count of joints with active disease among 71 joints; patient/parent global assessment of well-being (PGW) measured on a 0-10 visual analog scale (VAS) (0 = very well and 10 = very poor); physician global assessment of disease activity (PGA) measured on a 0-10 VAS (0 = no activity and 10 = maximum activity); and erythrocyte sedimentation rate (ESR). The ESR was normalized to a 0-10 point scale using the following formula: ESR (mm/h) – 20 / 10. An ESR of <20 mm/h was converted to 20 (equal to 0 on the 0-10 scale), while an ESR of >120 mm/h was converted to 120 (equal to 10 on the 0-10 point scale). The JADAS-71 was calculated by linear addition of the four component scores, yielding a global score of 0 to 101 (Consolaro *et al*, 2009).

All initial results of the complete blood count (CBC) were reviewed by a hematologist. Anemia was defined by World Health Organization criteria for anemia in children (WHO, 2011). Anemia of inflammation and IDA were diagnosed based on CBC results, peripheral blood smear,

reticulocyte count, serum iron concentration, total iron binding capacity, transferrin saturation, and ferritin concentration (Wians *et al*, 2001; Camaschella, 2015). Additional investigations, such as hemoglobin typing and direct antiglobulin testing, were performed at the hematologist's discretion if other causes of anemia, such as hemolytic anemia, were clinically suspected. Severe anemia was defined by anemia for age with the requirement for a blood transfusion (Sharma *et al*, 2011). Leukocytosis and leucopenia were defined as white blood cell (WBC) count >15,000/mm^3 and <4,000/mm^3, respectively. Neutropenia was defined as an absolute neutrophil count <1,500/mm^3. Neutrophilia was defined as an absolute neutrophil count >10,000/mm^3. Thrombocytopenia was defined as a platelet count <150,000/mm^3. Thrombocytosis was defined as a platelet count >450,000/mm^3. Macrophage Activation Syndrome (MAS) was diagnosed based on the preliminary diagnostic guidelines for systemic JIA-associated MAS (Davi *et al*, 2014).

Data were analyzed using PASW Statistics for Windows version 18.0 (IBM, Armonk, NY). Data were compared using Mann-Whitney *U* test or Pearson's chi-square test, as appropriate. Correlations between variables were analyzed by Spearman's rank analysis. Data were presented as number and percentage or median and range. A *p*-value of <0.05 was regarded as being statistically significant. The protocol for this study was approved by the Siriraj Institutional Review Board (SiIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (503/2014).

RESULTS

Of 55 patients with JIA (34 girls and 21 boys), 18 (32.7%) had systemic JIA. Median age at diagnosis of JIA was 8.1 years (range: 1.3-14.8). Median age at onset of initial symptoms was 7.4 years (range: 0.8-14.6). The median number of active arthritis joints was 3 (range: 0-19). Median PGA and PGW was 5 (range: 1-10) and 5 (range: 0-10), respectively. Median ESR and C-reactive protein (CRP) concentration was 62 mm/h (range: 5-117) and 21.7 mg/l (range: 0.3-239.8), respectively. Median JADAS-71 at the time of diagnosis was 17.6 (range: 4.6-39.2) (Table 1).

The most common hematologic manifestations at the time of JIA diagnosis were anemia (83.6%), followed by thrombocytosis (43.6%) and leukocytosis (20.0%). Anemia of inflammation was present in 40 (86.9%) JIA patients with anemia. Other causes of anemia in our patients included coexisting anemia of inflammation and IDA (3 patients) and Coombs-positive hemolytic anemia (1 patient). Of four patients that required blood transfusion, all had systemic JIA. Three of those had MAS and one developed severe symptomatic anemia of inflammation (Hb 6 g/dl). All patients with rheumatiod factor (RF) RF-positive polyarthritis, 94.4% of those with systemic JIA, 75% of those with enthesitis-related arthritis, and 61.5% of those with oligoarthritis had anemia of inflammation at the time of JIA diagnosis. Two of three (66.7%) patients with unclassified JIA and half of patients with negative polyarthritis had anemia of inflammation (Table 2).

Median hemoglobin concentration in patients with systemic and non-systemic JIA was 9.1 g/dl (range: 6.0-12.6) and 11.3 g/dl (range: 7.4-15.8), respectively. Median WBC count in patients with systemic and non-systemic JIA was 14,370 cells/mm^3 (range: 3,500-61,500) and 9,010 cells/mm^3 (range: 5,000-18,200), respectively. Median neutrophil count in systemic and non-systemic JIA patients was 10,685 cells/mm^3 (range: 1,600-52,000) and 4,900 cells/mm^3 (range: 2,000-15,300), respectively. Platelet counts were relatively similar between patients with systemic and non-systemic JIA at a median of 453,000 cells/mm^3 (range: 72,000-1,050,000) and 405,000 cells/mm^3 (range: 249,000-816,000), respectively. At the time of JIA diagnosis, median ESR and CRP in systemic JIA patients was 85.5 mm/h (range: 11-117) and 75.9 mg/l (range: 19.9-239.9), respectively,

Table 1
Demographic and clinical characteristics of patients with juvenile idiopathic arthritis (JIA).

Characteristics	Patients with JIA (*N*=55)
Age (yr), median (range)	8.1 (1.3-14.8)
Female, *n* (%)	34 (61.8)
JIA subtype, *n* (%)	
Systemic	18 (32.7)
Oligoarthritis	13 (23.6)
Enthesitis-related arthritis	12 (21.8)
Polyarthritis, RF positive	5 (9.1)
Polyarthritis, RF negative	4 (7.2)
Undifferentiated	3 (5.4)
Disease parameters, median (range)	
Arthritis joint count	3 (0-19)
Physician global assessment of disease activity	5 (1-10)
Patient/parent global assessment of well-being	5 (1-10)
ESR, mm/h	62 (5-117)
CRP, mg/l	21.7 (0.3-239.8)
JADAS-71	17.6 (4.6-39.2)

RF, rheumatiod factor; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; JADAS-71, Juvenile Arthritis Disease Activity Score -71; RF, rheumatoid factor.

while the median ESR and CRP in non-systemic JIA patients was 56.6 mm/h (range: 5-116) and 24.2 mg/l (range: 0.3-236), respectively. ESR and CRP concentration was significantly higher in patients with systemic than non-systemic JIA (p=0.001 *vs* p<0.001, respectively). Moreover, children with systemic JIA tended to have lower hemoglobin concentrations (p<0.001), higher WBC counts (p=0.001), and higher neutrophil counts (p<0.001). All patients with systemic JIA had anemia at initial presentation. Severe episodes of anemia that required blood transfusion occurred in 22.2% of patients with systemic JIA. Three patients (16.6%) with systemic JIA also had MAS at presentation. Leukocytosis, neutrophilia, and thrombocytosis were present in half of all systemic JIA patients. One patient with systemic JIA had thrombocytopenia. Patients with systemic JIA had significantly more anemia (p=0.023), severe anemia requiring blood transfusion (p=0.008), MAS (p=0.031), leukocytosis (p<0.001), and neutrophilia (p<0.001) than non-systemic JIA patients (Table 3).

Anemia of inflammation at the time of JIA diagnosis was associated with higher ESR (p<0.001) and CRP (p<0.001) concentrations. Age at diagnosis, duration of delayed diagnosis, arthritis joint count, PGA, and PGW were not significantly associated with anemia of inflammation (Table 4). Hemoglobin level was negatively correlated with arthritis joint count (r=-0.171), PGA (r=-0.084), PGW (r=-0.085), JADAS-71 (r=-0.351), ESR (r=-0.555), and CRP

Table 2
Hematologic manifestations at time of diagnosis in patients with Juverile idiopathic arthritis (JIA).

Hematologic manifestations	Patients with JIA, (*N*=55) *n* (%)
Anemia	46 (83.6)
Anemia of inflammation	40 (86.9)
Anemia requiring transfusion	4 (8.6)
Coombs-positive hemolytic anemia	1 (2.2)
Iron deficiency anemia	2 (4.3)
Combined anemia of inflammation and iron deficiency anemia	3 (6.5)
Leukocytosis (>15,000/mm^3)	11 (20)
Leukopenia (<4,000/mm^3)	1 (1.8)
Neutrophilia (>10,000/mm^3)	9 (16.4)
Neutropenia (<1,500/ mm^3)	1 (1.8)
Thrombocytosis (>450,000/mm^3)	24 (43.6)
Thrombocytopenia (<150,000/mm^3)	1 (1.8)
Macrophage activation syndrome (MAS)	3 (5.4)

concentration (*r*=-0.536). Inverse correlations between hemoglobin and ESR and hemoglobin and CRP are shown in Figs 1 and 2, respectively.

DISCUSSION

Hematologic involvement in JIA is frequent and clinically important. Hematologic complications can adversely affect patient quality of life, and some (particularly MAS) require prompt recognition and urgent treatment. In the present study, hematologic involvement at the time of JIA diagnosis was found in 87.3% of patients. Observed in 83.6% of patients, anemia was the most common hematologic finding. The most common cause of anemia was anemia of inflammation, which results from several mechanisms, including cytokine-driven dyserythropoiesis, hepcidin-induced hypoferremia, and a shortened erythrocyte lifespan (Nemeth and Ganz, 2014).

Studies of anemia in JIA are lacking. Few studies that investigated anemia complications in Asian JIA populations were conducted in India and Saudi Arabia (Seth *et al*, 1996; Al-Hemairi *et al*, 2016). The incidence of anemia in our study was higher than the rates reported by Seth *et al* (1996) of 40.8% and Kivivuori *et al* (2000) of 50%. This disparity in anemia incidence rates between studies may be due to the heterogeneity of JIA subtypes among these studies. One-third of patients in the present study had systemic JIA, while patients in the identified previous studies had more polyarticular arthritis. The present study revealed that patients with systemic JIA had a higher prevalence of anemia, severe anemia requiring blood transfusion, leucocytosis, neutrophilia, and MAS than patients with non-systemic JIA. Anemia requiring blood transfusion was found in 7.3% of patients, all of whom had systemic JIA. This may be explained by the effect of inflammatory cytokines *ie*, high plasma interleukin-6 in systemic JIA patients induced hepcidin production resulting in anemia of inflammation, which is a principle pathophysiologic mechanism of systemic JIA (Cazzola *et al*, 1996; Lin *et al*, 2011; Bruck *et al*, 2015).

Table 3
Comparison of hematologic involvement between patients with systemic and non-systemic juvenile idiopathic arthritis (JIA).

	Systemic JIA % (*n*=18)	Non-systemic JIA % (*n*=37)	*p*-value
Anemia, *n* (%)	18 (100.0)	28 (75.7)	**0.023**
Anemia of inflammation	15 (83.3)	25 (89.3)	0.569
Anemia requiring transfusion	4 (22.2)	0 (0.0)	**0.008**
Coombs-positive hemolytic anemia	1 (5.6)	0 (0.0)	0.216
Iron deficiency anemia	0 (0)	2 (10.7)	0.256
Combined anemia of inflammation and iron deficiency anemia	2 (11.1)	1 (3.6)	0.323
Leukocytosis, *n* (%)	9 (50.0)	2 (5.4)	**<0.001**
Leukopenia, *n* (%)	1 (5.5)	0 (0.0)	0.327
Neutrophilia, *n* (%)	9 (50.0)	0 (0.0)	**<0.001**
Neutropenia, *n* (%)	1 (5.5)	0 (0.0)	0.327
Thrombocytosis, *n* (%)	10 (55.5)	14 (37.8)	0.214
Thrombocytopenia, *n* (%)	1 (5.5)	0 (0.0)	0.327
Macrophage activation syndrome (MAS), *n* (%)	3 (16.7)	0 (0.0)	**0.031**

Table 4
Comparison of JIA patients with and without anemia of inflammation.

	With anemia of inflammation (*n*=43)	Without anemia of inflammation (*n*=12)	*p*-value
Age (yr)	8.1 (1.3-14.9)	6.8 (1.5-14.7)	0.833
Duration of delayed diagnosis (mo)	2.2 (0-49.7)	4.1 (1.0-48.7)	0.219
Arthritis joint count	3 (0-19)	3 (1-6)	0.322
Physician global assessment of disease activity	5 (1-10)	4.5 (1-8)	0.071
Patient/parent global assessment of well-being	5 (1-10)	5 (0-8)	0.470
ESR, mm/h	69 (11-117)	31 (5-67)	**<0.001**
CRP, mg/l	34.6 (91-239.9)	8.1 (0.3-33)	**<0.001**
JADAS-71	20.2 (8.7-39.2)	15.3 (4.6-23.4)	**0.003**

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; JADAS-71, Juvenile Arthritis Disease Activity Score -71.

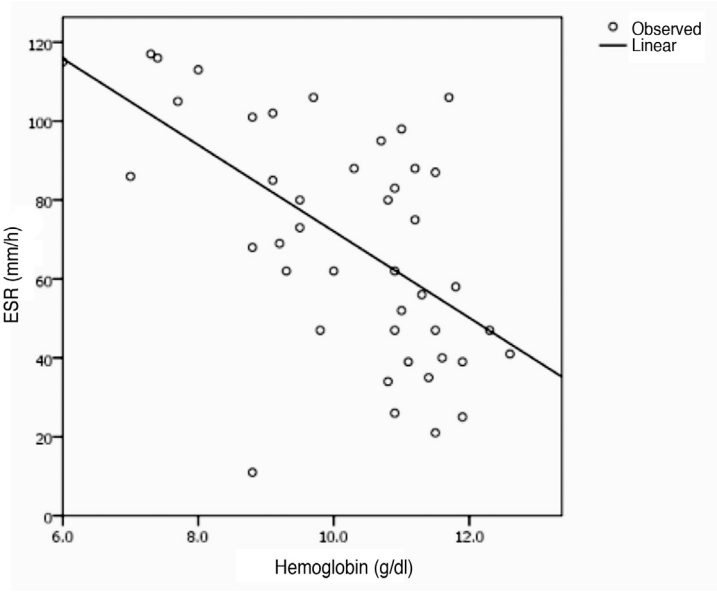

Fig 1– An inverse correlation was observed between hemoglobin (Hb; g/dl) and erythrocyte sedimentation rate (ESR; mm/h) in Thai patients with JIA (R^2=0.339).

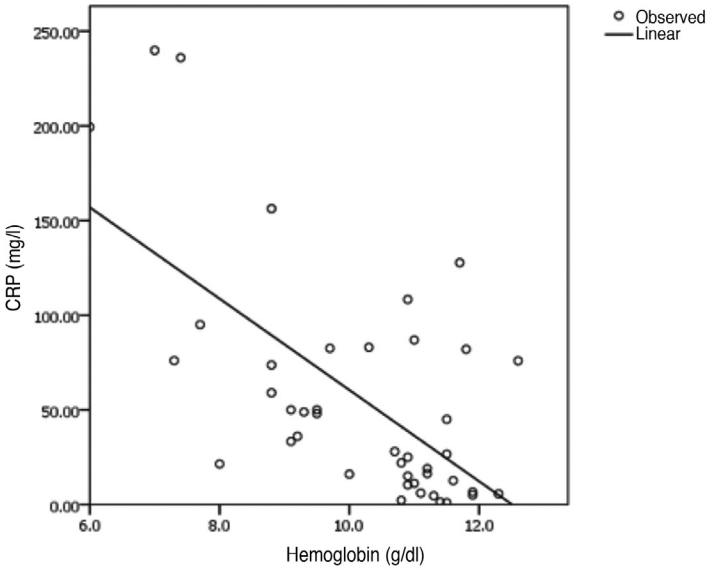

Fig 2– An inverse correlation was observed between hemoglobin (Hb; g/dl) and C-reactive protein (CRP; mg/l) in Thai patients with JIA (R^2=0.402).

We also found that all patients with RF-positive polyarthritis, and the majority of patients with enthesitis-related arthritis had anemia of inflammation. Additionally, in a previous report, only approximately half of patients with systemic juvenile rheumatoid arthritis (JRA) and one-third of those with pauciarticular and polyarticular JRA were anemic (Seth *et al*, 1996). In this study, we postulated that patients with JIA may have greater disease severity and a longer elapsed

time to diagnosis, resulting in a higher degree of anemia of inflammation (McErlane *et al*, 2016). However and specific to disease activity, our findings demonstrated that only higher disease activities based on ESR and CRP concentrations were associated with anemia of inflammation.

A review of adults with rheumatoid arthritis (RA) showed a correlation between anemia and disease duration, the number of American College of Rheumatology criteria for RA, a disease activity score of 28, swollen and tender joint count, erosive joint count, serum RF concentration, acute phase reactants, serum tumor necrosis factor-alpha and interleukin-1 beta concentrations (Peeters *et al*, 1996; Ganna, 2014). However, arthritis joint count, PGA, and PGW in our study were not significantly associated with severity of anemia, which is in contrast to the results reported from a study by Smyrnova (2014). That study found a significant negative correlation between hemoglobin level and arthritis joint counts in adults with RA. Subtypes of JIA were represented in our study population, with most having systemic JIA, oligoarthritis, or enthesitis-related arthritis. As a result, our patients were more likely to have lower arthritis joint counts at onset of disease. Therefore, a correlation between degree of anemia of inflammation and arthritis joint count might not be clearly observable in our study.

This study has some mentionable limitations including the small number of patients from a single tertiary center and a retrospective data collection. We are aware of some concerns regarding possible overlap between IDA and anemia of inflammation. However, all CBC results were thoroughly reviewed by a hematologist, and iron studies were performed to discriminate between these two conditions. Additionally, some previous reports found higher disease activity in those with anemia of chronic disease than in those with IDA (Vreugdenhil *et al*, 1992 a, b; Camaschella, 2015). Heterogeneity of JIA is an inherent complication when interpreting outcomes in JIA studies.

In conclusion, anemia of inflammation was found in most JIA patients in this study. Hematologic involvement among patients with systemic JIA was more prevalent and more severe than in those with non-systemic JIA. Hemoglobin level was negatively correlated with JIA disease activity parameters, most of which were acute-phase reactants. Early and aggressive treatment of JIA should result in reduced hematologic complications in patients with JIA.

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CONFLICTS OF INTEREST

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

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