Anemia of Chronic Disease in Rheumatoid Arthritis and its Relationship with Disease Activities

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Anemia is a frequent cause of morbidity in patients with rheumatoid arthritis (RA) that reduces quality of life. This observational cross sectional study was carried out in Rheumatology OPD and Medicine Indoor of Dinajpur Medical College Hospital, Dinajpur for duration of two years from January 2009 to December 2010 to find out the frequency of anemia of chronic disease (ACD) and relative frequency of pure ACD and ACD with co-existent iron deficiency anemia (IDA) in RA and to describe the relationship between ACD and disease activity of RA patients. For this purpose a total of 130 RA patients were enrolled according to the inclusion and exclusion criteria of the study and divided into anemia of chronic disease (ACD) group and non anemic group on the basis of hemoglobin level (≤ 11g/dl in females and ≤12 g/dl in males). ACD group of patients again divided into pure ACD and ACD with co-existent iron deficiency anemia (IDA) subgroups on the basis of ratio of soluble transferrin receptor (sTfR) to log ferritin (sTfR-F index). Patients with sTfR-F index value < 1 were classified as pure ACD and sTfR-F index value > 1 were classified as ACD with co-existent IDA. Disease activity was assessed by modified disease activity score (DAS-28), Tender Joint Count, Swollen Joint Count, morning stiffness in minutes, Health Assessment Questionnaire (HAQ), ESR in mm in 1st hour and RF positivity. Out of 130 patients, estimated frequency of ACD was 59%. Among the ACD patients, 16% were found to have pure ACD and 84% had both ACD and IDA. Disease activity parameters were compared between ACD group and non anemic group and than pure ACD and ACD with co-existent IDA subgroups of patients. We found significantly higher mean DAS-28 score, tender joint count, swollen joint count, HAQ score and mean ESR in ACD group of patients as compared to non anemic RA patients. When differing levels of disease activity indices were compared, we also found significant difference between ACD and non anemic groups. Patients with pure ACD subgroups had significantly higher mean DAS-28, tender joint count, swollen joint count and HAQ score as compared to ACD with co-existent IDA subgroups of patients. When comparing differing levels of disease activity indices, no significant difference was observed between pure ACD and ACD with co-existent IDA patients with RA. Thus it can be said in conclusion that ACD is frequently encountered with high frequency of iron deficiency anemia among rheumatoid arthritis patients. RA patients with ACD tend to have severe disease than non anemic RA patients but pure ACD patients not necessarily had severe disease as compared to combined ACD and IDA.

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Key words: Rheumatoid arthritis, ACD, IDA.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology characterized by symmetric erosive synovitis and in some cases extra-articular involvement.[1] Anemia is a common extra-articular manifestation of rheumatoid arthritis (RA) that reduces quality of life.[2] Anemia is also a cause of morbidity in patients with rheumatoid arthritis (RA), which is a prototypic disease of anemia of chronic disorder (ACD), although other causes of

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anemia such as iron deficiency anemia (IDA) can co-exist.[3] In various cross sectional studies, ACD has been reported to be presented in 30% to 70% of patients with RA.[4-8] In an Indian study, prevalence of Anemia in RA is 71% which is higher than western countries.[9] The difference in prevalence rate in various studies is related to the difference in the definition of anemia. Improvement in hemoglobin levels is associated with significant improvement in quality of life of anemic patients with RA.[10] It is important to identify ACD with concomitant IDA in RA since patients will benefit symptomatically by therapy with iron. According to various studies conducted in developed countries, iron deficiency was found in 30-60% of RA patients.[6,11,12] Iron therapy in RA patients without iron deficiency may aggravate arthritic symptoms as well as fail to manage anemia.[13] Identification and differentiation of anemia in RA is important in planning diagnostic and therapeutic modalities. The tests most commonly used are serum ferritin, serum iron/total iron binding capacity (TIBC), mean corpuscular volume (MCV), and reticulocyte count. In the general population, serum ferritin has been used as the most reliable indicator of iron deficiency.[14] However, ferritin is one of the acute phase reactants and its concentration in serum is influenced by various clinical conditions.[5] In evaluating accurate body iron status in patients with RA, the examination of stainable iron in bone marrow aspirate is the gold standard.[3] However, bone marrow examination can not be performed routinely in clinical practice for the sole purpose of diagnosing IDA or ACD because this procedure is invasive, expensive and time consuming. The soluble transferrin receptor (sTfR) has been introduced as a promising new diagnostic tool for differentiating between iron deficiency anemia (IDA) and anemia of chronic disease (ACD).[15-17] It is the truncated form of cell surface transferrin receptor, which causes the internalization of iron in erythroid cells. sTfR is increased in IDA as compared to ACD and has role in classifying the type of anemia.[18] Studies indicate that logarithmic transformation of the ferritin values and calculation of sTfR/log ferritin ratio (sTfR-F index) provides and outstanding indicator of iron depletion.[16,19]

The measurement of disease activity in rheumatoid arthritis (RA) has a long history. A variety of instruments have been described and used for this purpose, including various types of joint counts, acute phase reactants, global assessment scales, pain, fatigue and even more general measures such as anemia, hemoglobin or body weight. No single measure can reliably capture disease activity in all RA patients. Several composite indices are available to measure rheumatoid arthritis activity on continuous scale.[20] The modified DAS (DAS 28) is used extensively to evaluate disease activity in patients with RA. DAS 28 is based on counts of tender and swollen joints (28 joints), the patients global assessment of disease activity and the erythrocyte sedimentation rate (ESR). It is easier to perform than the 66/68 joint and it address the joints that are critically involved.[21]

Patients with rheumatoid arthritis who have anemia (ACD) are likely to have more severe disease as reflected by high disease activity score than patients without anemia.[8,22,23] There are number of reports from different studies observed that anemia of chronic disease (Pure ACD) has been found to be associated with greater disease activity than iron deficiency anemia (IDA) of rheumatoid arthritis patients.[8,9,24]

In this background attempt has been made to find out the frequency of anemia of chronic disease (ACD) among rheumatoid arthritis

patients and also describe the relationship between ACD with disease activity of rheumatoid arthritis.

Methods

This observational cross-sectional study was conducted in the Rheumatology OPD and Medicine Indoor, Dinajpur Medical College Hospital, Dinajpur for duration of two years from January 2009 to December 2010.

A total of 130 patients were included by convenience sampling who fulfilled the American College of Rheumatology (ACR) 1987 revised diagnostic criteria for RA.[25] Patients with known malignancies, renal failure, hemolytic conditions, patients received iron treatment or blood transfusion within one month, macrocytosis and chronic blood loss not related to RA such as hemorrhoids and fissures were excluded from the study. All the patients were given an explanation of the study and informed written consent was taken before enrollment into the study. Data was collected by taking history, doing examination and performing some relevant investigations. Demographic details included age, sex, marital status, occupation, educational qualification, family history and duration of disease etc were recorded. Disease activity related characteristics were recorded for all patients included tender joint count, swollen joint count, duration of early morning stiffness, Bengali health assessment questionnaire etc. Modified disease activity score (DAS 28) was calculated. Apart from these the use of disease modifying anti-rheumatic drugs (DMARDs), NSAIDs and oral corticosteroids were also recorded. Laboratory work up included complete blood count (CBC), erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), peripheral blood film (PBF), retuculocyte count, RA test, serum ferritin (estimated by particle enhanced immunonephelometry using the BN system), soluble transferrin receptor (measured by particle enhanced immunoturbidimetric assay, roche/Hitachi analyzer) and serum creatinine, soluble transferrin receptor (sTfR)/log ferritin ratio (sTfR-F index) was then calculated.

At the end of study, patients were divided into anemia of chronic disease (ACD) and non anemic group on the basis of hemoglobin level ($\leq$11 gm/dl in females and $\leq$ 12 gm/dl in males). Then frequency of ACD was determined. Patients with ACD were further subdivided into pure ACD and ACD with co-existent iron deficiency anemia (IDA) subgroups on the basis of sTfR-F index. (sTfR-F index value <1 for pure ACD and >1 for ACD with co-existent IDA).[19] Comparison of quantitative and qualitative variables of disease activity between two group and sub groups were analyzed by student's 't' test and chi-square test respectively. P value of less than 0.05 was regarded as significant. All collected data was analyzed by using computer based software SPSS (Statistical Package for Social Science), version- 14.

Results

Out of 130 patients, ACD was present in 77 (59%) of RA patients and the remaining 53 (41%) patients were non anemic. Among the patients with ACD, 12 patients (16%) were found to have pure ACD and 65 (84%) had concomitant ACD and IDA.

The socio-demographic characteristics of RA patients are summarized in Table I. Mean (±SD) age was 41.2±12.2 years. Out of 130 patients, 110 (84.6%) were female and 20 (15.4%) were male and female to male ratio was about 5.5:1.

Comparison of disease and disease activity related characteristics between ACD and non anemic RA patients and then between pure ACD and ACD with co-existent IDA patients are illustrated in Table II and III respectively.

DAS- 28 score (p< 0.001), tender and swollen joint count (P<0.001 for both tender and swollen joint count), ESR (p< 0.001) and HAQ score (p< 0.001) were significantly higher in ACD group of patients as compared to non anemic one. But there was no significant difference in terms of disease duration, morning stiffness and RF positivity between mentioned groups (p> 0.05) (Table- II). When comparing disease activity related characteristics between pure ACD and ACD with co-existent IDA sub group of patients, DAS 28 (p< 0.001), tender joint count (p= 0.03), swollen joint count (p= 0.03) and HAQ score (p= 0.03) were significantly higher in pure ACD patients than ACD and concomitant IDA patients with RA. But no significant difference was observed between two subgroups in terms of disease duration, morning stiffness, ESR and RF positivity (p> 0.05) (Table- III).

Comparison of disease activity indices at different cut off levels between two groups and subgroups are shown in Table- IV and V respectively. Higher DAS- 28 score, tender joint count, swollen joint count and HAQ score was significantly found in ACD group of patients as compared to non anemic one. No significant difference was found between two groups at differing levels of morning stiffness (p= 0.16) (Table- IV). When comparing mentioned disease activity indices at different cut off levels, no significant difference was observed in DAS- 28, morning stiffness, tender joint count, swollen joint count and HAQ score between pure ACD and ACD with co-existent IDA sub group of patients (Table- V).

Table I: Socio-Demographic Characteristics of RA patients (N=130)

		n (%)
Age in years	18-20	7 (5.4)
	21-30	20 (15.4)
	31-40	42 (32.3)
	41-50	33 (25.4)
	51-60	23 (17.7)
	61-70	5 (3.8)
	Mean±SD	41.2±12.2
Sex	Male	20 (15.4)
	Female	110 (84.6)
Education	Illiterate	38 (29.2)
	Primary	29 (22.3)
	Secondary	25 (19.2)
	Higher secondary & above	38 (29.2)
Marital status	Married	113 (86.9)
	Unmarried	9 (6.9)
	Others	8 (6.2)
Occupation	House wife	96 (73.8)
	Service	13 (10.0)
	Student	4 (3.1)
	Business	4 (3.1)
	Labour	3 (2.3)
	Others (Driver, Cultivator, Mechanic etc)	10 (7.7)
Family history	No	113 (86.9)
	Yes	17 (13.1)
	Total	130 (100.0)

Table II: Comparison of disease and disease activity related characteristics between ACD and non-anemic RA patients

Disease and disease activity parameters	ACD (n=77) Mean±SD	Non-Anemic (n=53) Mean±SD	*P-Value
Duration of disease (in month)◆	36(04-180)	36(06-180)	0.90
Hematological feature			
Hemoglobin (gm/dl)	9.2±1.2	12.1±1.1	< 0.001
MCV (fl)	78.2±9.5	88.3±5.6	0.88
MCH (pg)	24.3±3.9	28.7±2.2	0.88
MCHC (gm/dl)	30.0±1.8	33.5±8.1	0.29
Platelet count ($\times 10^9$/L)◆	350(162-610)	280(190-450)	< 0.001
Disease activity parameters			
DAS 28	6.5±1.1	5.6±0.84	< 0.001
Tender Joint Count	31.6±11.9	21.3±9.0	< 0.001
Swollen Joint Count	4.4±3.7	1.9±2.4	< 0.001
Morning Stiffness (in minutes)◆	90(10-300)	60(10-180)	0.10
HAQ	1.3±.83	.83±0..33	< 0.001
Erythrocyte Sedimentation Rate◆ (mm in 1st hour)	60(20-140)	40(10-105)	< 0.001
RF (Positive)#	51 (66.2)	31 (58.5)	0.37
Drug used#			
NSAID	77 (100.0)	48 (90.6)	0.01
Steroid	29 (37.7)	9 (17.0)	0.01
DMARD	42 (54.5)	19 (35.8)	0.04

*P values are based on unpaired 't' test /χ^2 test, #No. (%), ◆Median (range)

Table III: Comparison of disease and disease activity related characteristics between pure ACD and ACD with co-existent IDA patients

Disease and disease activity parameters	Pure ACD (n=12) Mean±SD	ACD+IDA (n=65) Mean±SD	*P-Value
Duration of disease (in month)◆	30(09-120)	36(04-180)	0.16
Hematological feature			
Hemoglobin (gm/dl)	9.9±0.6	9.0±1.3	0.03
MCV (fl)	85.6±4.4	76.4±9.6	< 0.001
MCH (pg)	26.4±1.4	23.8±4.1	0.03
MCHC (gm/dl)	30.8±0.9	30.8±7.8	0.98
Platelet count ($\times 10^9$/L) ◆	340(240-450)	350(160-610)	0.99
Disease activity parameters			
DAS 28	7.2±0.3	6.5±0.8	< 0.001
Tender Joint Count	38.3±6.7	30.5±12.1	0.03
Swollen Joint Count	6.6±2.7	4.0±3.8	0.03
Morning Stiffness (in minutes) ◆	90(30-240)	90(30-300)	0.65
HAQ	1.6±0.5	1.3±0.5	0.03
Erythrocyte Sedimentation Rate◆ (mm in1st hour)	60(50-110)	65(20-140)	0.61
RF (Positive)#	7(58.8)	44(67.7)	0.81
No (%)			
Drug used#			
No. (%)			
NSAID	16(100.0)	65(100.0)	
Steroid	1(8.3)	29(44.6)	0.03
DMARD	6(50.0)	34(56.9)	0.65

*P values are based on unpaired 't' test /χ^2 test, #No. (%), ◆ Median (range)

Table IV: Comparison of disease activity indices at different cut-off levels between ACD and non anemic RA patients

Disease activity indices	ACD (n=77)	Non anemic (n=53)	P value*
DAS-28			
3.2 – 5.1	6(7.8)	11(20.8)	0.015
> 5.1	71(92.2)	42(79.2)	0.015
Morning stiffness (in min)			
< 60	34(44.2)	28(52.8)	0.167
≥ 60	43(55.8)	25(47.2)	0.167
Tender joint count			
0-10	2(2.6)	5(9.4)	0.04
10-20	14(18.2)	22(41.5)	0.002
20-30	28(36.4)	15(28.3)	0.16
≥ 30	33(42.9)	11(20.8)	0.004
Swollen joint count			
0-10	73(94.8)	53(100.0)	0.04
10-20	4(5.2)	0(0.0)	0.04
HAQ			
0-1	25(32.5)	47(88.7)	< 0.001
1-2	45(58.4)	6(11.3)	<0.001
2-3	7(9.1)	0(0.0)	0.012

Values are No. (%), *p values are based on chi-square (χ^2) test.

Table V: Comparison of disease activity indices at different cut-off levels between pure ACD and ACD with co-existent IDA patients with RA

Disease activity indices	Pure ACD (n=12)	ACD+IDA (n=65)	P value*
DAS-28			
3.2 – 5.1	0(0.0)	5(7.7)	0.16
> 5.1	12(100.0)	60(92.3)	0.16
Morning stiffness (in min)			
< 60	6(50.0)	27(41.5)	0.298
≥ 60	6(50.0)	38(58.5)	0.292
Tender joint count			
0-10	0(0.0)	1(1.5)	0.337
10-20	0(0.0)	15(23.1)	0.032
20-30	2(16.7)	26(40.0)	0.062
≥ 30	10(83.3)	23(35.4)	0.001
Swollen joint count			
0-10	11(91.7)	62(95.4)	0.298
10-20	1(8.3)	3(4.6)	0.298
HAQ			
0-1	2(16.7)	23(35.4)	0.102
1-2	8(66.7)	37(56.9)	0.263
2-3	2(16.7)	5(7.7)	0.160

Values are No. (%), *p values are based on chi-square (χ^2) test

Discussion

This cross-sectional study observed the frequency of ACD and the relative frequency of co-existent IDA in rheumatoid arthritis patients similar to previous studies[3,7,9]. We observed higher prevalence of disease activity indices in ACD patients with RA as compared to non-anemic RA patients. Using cut off levels of different severity indices of RA did not show significant differences in the prevalence of pure ACD and ACD with co-existent IDA.

In our study estimated frequency of ACD was 59%. In various cross sectional studies, ACD has been reported to be present in 30% to 70% of patients with RA.[4-7] The difference in prevalence rate in various studies is related to the difference in the definition of anemia. In India, Borah et al.[20] showed that anemia (ACD) was present in 64% of patients, which is nearly comparable to our study. If the WHO criterion (men Hb $\leq$ 13gm/dl and women $\leq$ 12g/dl) has been used to define anemia, frequency of ACD in our study would be 84.6% which is much higher than prevalence reported in RA patients from western countries. This may be related to high background prevalence of anemia in our country as well as poor access to medical care leading to poor disease control of RA. We excluded various causes of anemia such as renal failure, hemolysis, pregnant and lactating mother, menorrhagia, hemorrhoids etc. otherwise actual frequency of anemia in RA would be much higher.

Identification and sub-classification of anemia in RA may be important in planning diagnostic and therapeutic modalities. The definitive method to distinguish between IDA and ACD is the assessment of stainable iron in bone marrow which is invasive, expensive and time consuming.[3] We have tried to use soluble transferrin receptor /log ferritin ratio (sTfR-F index) which we have been described as a promising new diagnostic tool to sub-classify pure ACD and IDA in anemic RA patients. Patients with sTfR-F index value < 1 were classified as pure ACD and sTfR-F index value >1 were classified as ACD with co-existent IDA.[19] Using this criteria, 16% patients were found to have pure ACD and 84% patients had co-existent IDA and ACD. Almost similar results were observed in an Indian study.[3] Thus sTfR-F index should be utilized regularly to classify ACD when conventional laboratory test such as serum iron, transferrin /total iron binding capacity, transferrin saturation and serum ferritin are influenced by acute phase response.[19]

Ravindron et al.[24] showed that, among the anemic patients with RA, anemia was significantly worse in IDA group as compared to ACD group which was nearly similar to our study findings. Iron deficiency in RA is mainly related to non-steroidal anti-inflammatory drugs and steroid induced occult gastrointestinal blood loss. High female predominance (84.6%) and poor intake as well as other dietary factors may contribute to iron deficiency in RA patients from our study.

In present study, drug history that included NSAID, steroid and DMARD was also recorded and showed that anemic (ACD) RA patients more often received treatment with NSAID, steroid and DMARD's than non anemic patients. No significant difference was observed in taking drugs between pure ACD and ACD with co-existent IDA subgroups of patients. Intake of drugs particularly NSAID and steroid may contribute to development of anemia in RA patients.

We also assess disease activity in both anemic (ACD) and non anemic RA patients. A variety of parameters have been used for this purpose, including DAS-28, tender joint count, swollen joint count, Bengali HAQ,

morning stiffness, ESR, RF positivity etc. Agrawal et al.[9] and Borah et al.[20] found that anemic patients with RA had significantly higher mean DAS-28 score, tender joint count, swollen joint count, morning stiffness, mean ESR as compared to non anemic patients which was nearly comparable to our study. We also found significantly higher mean HAQ score in anemic (ACD) RA patients than non anemic patients with RA. Borah et al.[20] found similar study findings. Doube et al.[12] did not find statistically significant difference between mentioned groups in mean HAQ score. Agrawal et al.[9] also found significantly higher mean morning stiffness in anemic RA patients than non anemic one which was not correlated with our study findings. Mentioned disease activity indices were compared with different cut-off levels between two groups. Most ACD patients (92%) have higher cut-off levels of DAS-28 (> 5.1) though moderate levels of DAS-28 (3.2-5.1) was significantly higher in non-anemic group. In terms of HAQ score, maximum percentage (67.5%) of patients with ACD have higher HAQ score (>1) which indicate ACD patients with RA are more disabled than non-anemic one. Tender and swollen joint count when compared with different cut-off levels was found to be significantly higher in RA patients with ACD. So it can be said that when disease activity indices were compared with mean values and different cut-off levels, it may reveal RA patients with ACD are more active as compared to non anemic one.

Mentioned disease activity parameters were also compared between pure ACD and ACD with co-existent IDA subgroups of patients with RA. We observed that patients with pure ACD had higher DAS-28 score, tender joint count, swollen joint count and HAQ score as compared to ACD with co-existent IDA sub group of patients with RA. The results were similar to that of other study.[9] Our study did not find significant difference in morning stiffness between mentioned subgroups which was almost similar to another study conducted by Doubel et al.[12]. But Agrawal et al.[9] found significantly higher morning stiffness in pure ACD group of patients than IDA patients with RA. When mentioned disease activity indices were compared between two subgroups with differing levels of disease activity, we found no significant difference between pure ACD and ACD with co-existent IDA patients with RA. This may be possibly due to smaller scale study in a tertiary hospital which may not represent whole population & interruption of disease activity by irregular intake of multiple drugs.

The limitation of this study is that firstly sample size was smaller than calculated due to limitation of time and financial constrains. Secondly this study was conducted in the single center over a short period of time which may not have allow diverse RA population. It is expected that in such a center, patients usually having severe disease, refractory disease with complications, thereby prevalence rate may be over or underestimated. Thirdly, presence of too many confounding variables may influence anemia and hemoglobin level. Thereby some important causes of anemia such as DMARD induced anemia, thalasemia trait could not be eliminated.

Thus it can be concluded that ACD is frequently encountered with high frequency of iron deficiency anemia among rheumatoid arthritis patients. RA patients with ACD tend to have severe disease than non anemic RA patients but severity of disease activity has got no difference between pure ACD and ACD with co- existent IDA patients with RA. Multi-centre large scale studies are needed to increase the power of the study.

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