



## A STUDY ON INCIDENCE OF PATHOLOGIES THEIR ASSOCIATIONS IN ANEMIA OF CHRONIC DISEASE

### Pathology

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### ABSTRACT

**BACKGROUND:** Anemia of chronic disease (ACD) is the second most prevalent anemia overall after iron deficiency anemia which develops under the setting of chronic infections, cancer or autoimmune diseases. Detection of the type of anemia is important to execute a correct treatment plan. Identification of anemia of chronic disease will definitely have great impact on treatment. **MATERIAL AND METHODS:** This is Prospective Study total 100 cases of age group between 18-80 years having chronic illnesses attending the outpatient clinic as well as admitted in Darbhanga medical college and Hospital Laheriasarai, Bihar. with hemoglobin <13 g/dl (haematocrit <39%) in men and women with hemoglobin <12g/dl (haematocrit <36%) between the study period of two years were included in the study. **CONCLUSION:** ACD is a unrecognized problem and diagnosis of ACD is the need of an hour. Thus, the present study was undertaken, keeping this need in view.

### KEYWORDS

Anemia of Chronic Disease, Incidence, Frequency.

### INTRODUCTION

Anemia is the most common haematological disorder, a global problem of immense health significance. Anemia of chronic disease (ACD) is the second most prevalent form of anemia after iron deficiency anemia (IDA).<sup>1</sup> Anemia of chronic disease (ACD) is a hypo proliferative anemia occurring in chronic infectious, inflammatory or neoplastic disorders. ACD is characterized by mild (> 100 g/L) or moderate (85–100 g/L) reductions in hemoglobin concentrations. In a minority of patients, severe reductions can occur. This mild to moderate normocytic to microcytic anemia is found with a frequency between 8% and 95%. The estimated prevalence of anemia of chronic disease caused due to chronic inflammation accounts to 23-50%. The condition has thus been termed as "anemia of inflammation". ACD in chronically ill patients has a negative impact on quality of life as well as survival, the ability to diagnose this disorder depends on the ability of the physician to correlate the possible clinical pathways of underlying disease with patients ferrokinetic state. The cytokines and acute phase proteins play an important role in pathogenesis of ACD. Hepcidin molecule has the ability to reduce the function of ferroportin on duodenal enterocytes, macrophages, placental cells and hepatocyte, which leads to impaired iron absorption from the gut and exaggerated iron retention, which is a hallmark of anemia of chronic disease. The present study was undertaken to highlight the incidence of chronic illnesses, morphological patterns and association thereof in anemia of chronic disease, to establish anemia in chronic diseases using lab parameters like serum ferritin, serum iron, total iron binding capacity. ACD is quite often neglected or improperly treated. Detection of the type of anemia is important to execute a correct treatment plan. Anemia of chronic disease is quite distinct due to the fact that it is not as a result of deficiency but due to factors impeding the availability of iron, inflammation is one such impeding factor causing anemia of chronic disease. Mere removal or reduction of inflammation may not correct the anemic status. It has to be supported with appropriate therapy. The study focuses on aspects like incidence, morphological pattern and their frequency of association in anemia of chronic disease, a correct identification of anemia of chronic disease will definitely have great impact on treatment. Hepcidin has emerged as one such molecule which has caught the attention of researchers.

### OBJECTIVES

To evaluate the incidence of chronic illnesses manifesting as anemia of chronic disease.

### Review of Literature

In 1989 Cash and Sears evaluated all patients admitted to the medicine ward by screening them for anemia. All the patients were divided into three groups on the basis of serum values indicating the iron distribution into Iron deficiency anemia, ACD and all others (non-ACD). The Seven patients with iron deficiency were not considered

further. Ninety patients with ACD were compared with 75 patients with non-ACD. The anemia in ACD patients was more severe. The mean haematocrit was 31% and 20 patients had haematocrit below 25%. The anemia was usually normocytic (mean red cell volume [MCV] 86 fL), but 21% had an MCV less than 80 fL. Anemia is defined by a decrease in the total amount of hemoglobin or the number of red blood cells. The World Health Organization (WHO) defined anemia as a hemoglobin <13 g/dl (haematocrit <39%) for adult males and hemoglobin <12 g/dl (haematocrit <36%) for adult non-pregnant females.

Anemia of chronic disease is usually a mild to moderate anemia (hemoglobin rarely lower than 8 g/dL) that develops in infection, inflammatory disease or malignancy.

The defining features of ACD include low serum iron despite adequate systemic iron stores. The erythrocytes are usually of normal size and have normal hemoglobin content but are reduced in number (normocytic, normochromic anemia). In normal healthy individuals, the amount of body Fe is maintained within a range of 4–5g by a strict control of its absorption, mobilization, storage, and by recycling. The body has no effective means of excreting iron and hence the regulation of absorption of dietary iron from the duodenum plays a critical role in iron homeostasis in the body. Dietary iron is found in two forms i.e. haem and ionic (non-haem). Absorption of iron occurs at the apical surface of duodenal enterocytes. Dietary non-haem iron exists in an oxidised (Fe<sup>3+</sup>) form primarily and that is not bioavailable, hence it must first be reduced to the Fe<sup>2+</sup> form before it can be transported across the intestinal epithelium. This is done by ferrireductase enzyme, a membrane bound haemoprotein called Dcytb expressed in brush border of the duodenum. Anemia is a common comorbidity at tuberculosis diagnosis, with prevalence ranging from 32% to 86%. Large proportion of TB-associated Anemia is due to ACD, most studies have shown suppression of erythropoiesis by inflammatory mediators as a cause of anemia. Minchella PA *et al* conducted a study on 45 patients with confirmed pulmonary tuberculosis (cases), 47 tuberculin skin test (TST)-positive controls, and 39 TST- negative controls in Gambia and measured baseline hemoglobin, ferritin, hepcidin, soluble transferrin receptor (sTfR), and transferrin. Anemia was more frequent in tuberculosis cases (67%) than in TST-positive (36%) or TST-negative (21%) controls. Anemia of chronic disease was the predominant anemia at tuberculosis diagnosis, declining from 36% to 8% after 6 months of treatment, Anemia of inflammation accounted for 45% (n = 23/51) of anemia among all participants (combined tuberculosis, TSTnegative, TST-positive) and was the most common anemia. When ACD is associated with a true iron deficiency, iron therapy is the first choice of treatment. In addition, considering iron blockage into the RES as a potentially effective defense strategy to inhibit the growth of pathogens. Iron therapy can increase the risk of

infection and can promote the highly toxic hydroxyl radical formation, strictly relating to the increased risk of acute cardiovascular events. For all these reasons, iron treatment can be effective in some patients with ACD.

## MATERIAL AND METHODS

This is Prospective Study total 100 cases of age group between 18-80 years having chronic illnesses attending the outpatient clinic as well as admitted in Darbhanga medical college and Hospital, Laheriasarai, Bihar. with hemoglobin <13 g/dl (haematocrit <39%) in men and women with hemoglobin <12g/dl (haematocrit <36%) between the study period of two years were included in the study.

**collection of data:** Samples for the study were selected according to the inclusion and exclusion criteria.

### Inclusion Criteria

Patient having chronic illnesses, Patient within age group range 18-80yrs. Men with haemoglobin <13g/dl (haematocrit<39%) and women with haemoglobin <12g/dl (haematocrit <36%).

### Exclusion Criteria

Previously diagnosed cases of thalassemia / sideroblastic anemia/lead poisoning/ iron deficiency anemia, Patients aged less than 18years, Patients with Congenital anemia's.

Blood samples were collected aseptically in EDTA and Plain vacutainers. EDTA vacutainers for hematological investigations. Plain vacutainers was used for serum ferritin, serum iron and TIBC. Serum was separated and taken for Serum Ferritin Assay, serum iron estimation and total iron binding capacity. As a part of complete blood count, Hb %, Packed cell volume(PCV), RBC count, RBC Indices (MCV, MCH, MCHC), Red cell distribution width (RDW), White Blood Cell Count & Platelet Count was analyzed using auto hematology analyzer mindray BC-3000 plus. Serum ferritin assay, Serum iron estimation and total iron binding capacity were done by biochemical methods.

Considering the prevalence of anemia of chronic disease due to chronic inflammation as 50%<sup>3</sup>. P=50, d=.01 with 95% confidence level, sample size was calculated using tables of minimum sample size proposed by WHO.

**Stastical Analysis:** Stastical analysis was done using mean, frequenc, percentages and standard deviation.

### Procedure

	Blank	Standard	Sample
Reagent	1000µL	1000 µL	1000MI
Distilled Water	40µL	-	-
Standard	-	40 µL	-
Sample	-	-	40µL

Mix and incubate for 10 minutes at room temperature. Measure the absorbance (A) of standard and sample against the reagent blank at 630 nm. The colour is stable for 1 hour when protected from light.

Calculations:

$$\text{Iron } (\mu\text{g/dL}) = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times 200$$

Mix and leave at room temperature for 10 minutes, then add one aliquote of reagent B and shake, leave at room temperature for 15minutes by shaking at regular intervals (4 times with vortex for 10-15 minutes). Centrifuge until you get a clear supernatant.

## RESULTS

In the present study we found out the incidence of chronic illnesses causing ACD, and association thereof in anemia of chronic disease on total 100 cases which satisfied the inclusion & exclusion criteria as per our study .

### Distribution Of Study Subjects According To Their Age

S No.	AGE DISTRIBUTION	NUMBER OF PATIENTS	PERCENTAGE (%)
1	21-30 YEARS	7	7 %
2	31-40 YEARS	14	14 %

3	41-50 YEARS	22	22 %
4	51-60 YEARS	32	32 %
5	61-70 YEARS	15	15 %
6	71-80 YEARS	10	10 %
	<b>TOTAL</b>	<b>100</b>	<b>100 %</b>

### Age And Sex Distribution Of Study Subjects

S No.	AGE DISTRIBUTION	MALE	FEMALE
1	21-30 YEARS	5 (5%)	2 (2%)
2	31-40 YEARS	8 (8%)	6 (6%)
3	41-50 YEARS	12 (12%)	10 (10%)
4	51-60 YEARS	25 (25%)	7 (7%)
5	61-70 YEARS	10 (10%)	5 (5%)
6	71-80 YEARS	6 (6%)	4 (4%)
	<b>TOTAL</b>	<b>66 (66%)</b>	<b>34 (34%)</b>

Among the 66 males studied, 25 belong to 51-60yrs age group followed by 12 in 41-50 yrs, 10 in 61-70yrs, 8 in 31-40 yrs, 6 and 5 in age group of 71-80 yrs and 21-30 yrs respectively. Among the 34 females studied, 10 belonged to 41-50 yrs, followed by 7 in 51-60 yrs, 6 in 31-40yrs, 5 in 61-40yrs and 4 and 2 in age group of 71-80yrs and 21-30yrs respectively. Amongst the predominant age group in the study population i.e. 51-60yrs, males constituted the maximum number.

### Red Cell Distribution Width In Patients With Anemia Of Chronic Disease

S No.	RED CELL DISTRIBUTION WIDTH	No. OF PATIENTS	PERCENTAGE (%)
1	< 11 %	1	1 %
2	11 – 16 %	91	91 %
3	> 16 %	8	8 %

Majority of the cases i.e. 91 cases (91%) in the study population had normal RDW with 8 cases (8%) having high RDW.

Among 100 cases of anemia of chronic disease studied, the most common morphological pattern of anemia on peripheral smear was Normocytic Normochromic (63%) followed by Microcytic hypochromic anemia in 21 cases (21%), and Normocytic hypochromic anemia in 16 cases (16%). The reticulocyte count was lower in 79 cases (79%) and it was normal in 21 cases (21%). This graph depicts majority of the cases i.e. 79 cases (74%) had lower reticulocyte count. Amongst the 100 cases studied, all the cases had serum iron below the normal range for the age and sex .Amongst 66 of male patients, all the 66 had their serum iron below 65 microgram/dL. Amongst the 34 female patient all the 34 had serum iron below 50 microgram /dL. 100 ACD cases, there were 37 tuberculosis cases, 20 cases (54%) had normocytic normochromic pattern, 11 (29.7%) had microcytic hypochromic pattern and 6 cases (16%) had normocytic hypochromic pattern.

Out of 23 cases of rheumatoid arthritis, 12 cases (52.17%) had normocytic normochromic pattern, 6 cases (26.08%) had normocytic hypochromic pattern and 5 cases (21.74%) had microcytic hypochromic pattern. 12 cases of HIV were present, 9(75%) had normocytic normochromic pattern, 2(16.66%) had normocytic hypochromic pattern and 1 (8.33%) had microcytic hypochromic pattern. In 8 Malignancy (Ca Breast) cases, 6(75%) had normocytic normochromic pattern and 2 cases (25 %) had microcytic hypochromic pattern. 7 COPD cases had 6 cases (85.7%) having normocytic normochromic pattern, 1(14.28%) had normocytic hypochromic pattern. In 7 SLE cases, 5 (71.43%) had normocytic normochromic pattern, 1(14.28%) had normocytic hypochromic pattern and 1(14.28%) had microcytic hypochromic pattern. Out of 4 Hodkins lymphoma cases, 3 (75%) had normocytic normochromic pattern and 1 (25%) had microcytic hypochromic pattern & in 1 Non Hodkins lymphoma cases, 1 (100%) had normocytic normochromic pattern.

## DISCUSSION

The present study was to establish the incidence of chronic illnesses causing anemia of chronic diseases, the morphological pattern of anemia in ACD, and the frequency of morphological patterns with the chronic illness in ACD. Once the clinical diagnosis was established based on clinical signs and symptoms. The laboratory features were resorted for. Diagnosis of ACD began with hemoglobin estimation, pattern manifest in peripheral smear and the erythrocyte indices for correlation, we had taken into account the parameters MCV and

Peripheral smear findings for the initial workup in cases with reduced hemoglobin. When pattern was normocytic, a reticulocyte count was considered. A low reticulocyte count prompted evaluation of WBC and platelet parameters which when at their lower limits bone marrow failure would be the case. We had normal to high counts which prompted us to consider the diagnosis of ACD. Serum iron, Serum ferritin, TIBC were performed in these cases. All the cases had normal to increased serum ferritin, normal to decreased TIBC, and decreased serum iron. With the microcytic pattern a normal and high serum ferritin level prompted evaluation of serum iron level and TIBC, a decreased serum iron level and decreased and normal TIBC suggested ACD. Whereas IDA was ruled out which will have serum iron level decreased with increased TIBC. In the present study, moderate degree of anemia was found in maximum number of cases (62%) which is in concurrence with the study by Ikram N *et al* (45%) where moderate degree of anemia was the most prevalent type.

Most of the cases are in moderate range of hemoglobin probable reason could be that those having chronic illness manifest with symptoms early in the course of the disease process. Only a modest decline in haemoglobin levels are noted over a period of time due to shuttling of iron to ferritin form as a defense mechanism in order to shut down the nutrition to harmful pathogens which happens under the influence of cytokines. In the present study mean MCV was 83.9, Cash *et al* <sup>11</sup> concluded in a study conducted on 90 patients of ACD that mean red cell volume was 86 fl. MCV is a good indicator of ACD when in normal range, when reduced the other studies like peripheral smear, RDW, serum ferritin, TIBC, serum Iron has to be considered to rule out other cause of anemia.

In the present study the mean MCH was 27.09 and was in the range of 27.09±1.76 which was concordant with the study conducted by Wians Jr FH *et al* with hemoglobin range of 29.5±2.9. study conducted on 90 patients of ACD that the anemia was usually normocytic (mean red cell volume [MCV] 86 fL), but 21% had an MCV less than 80 fL. We made an effort to correlate the hemoglobin & serum ferritin level with the morphological pattern. Out of 63 cases of NCNC pattern, hemoglobin decrease was predominantly mild to moderate suggesting a recent onset of disease. Only one of the case had severe decrease in hemoglobin levels. Their serum ferritin levels were normal in 43 cases (68%) and increased in 20 cases (32%). Out of 21 cases of MCHC, 4 cases had hemoglobin less than 8 (severe anemia). Normal ferritin was seen in 15 cases (71.25%) and increased ferritin in 6 cases (28.57%) There was a good correlation of hemoglobin level as far as NCNC pattern was considered, where most of that had mild to moderate decrease in hemoglobin, whereas the one with MCHC pattern did not have the expected decreased level of hemoglobin. Most of that had hemoglobin in moderate range (8-9.5g/dl).

Despite the progression of disease with resulting change in pattern, the fluctuations in the serum ferritin levels remains unchanged. This might perhaps be due to intervention by drugs. Anemia is a common in TB. The majority of the cases in the present study were of Tuberculosis (37%). A Study conducted by Ikram N *et al* found that TB was the commonest of the known causes i.e. 6 cases (17%) out of 35. Mukherjee A *et al* conducted a study on 246 patients with pulmonary TB, 176 patients were anemic with anemia of chronic disease in 103 patients. Oliveira *et al* studied 166 patients of TB, 148 (89%) were anemia ACD was the most common and was found in 126 (75.9%) patients. Minchella PA *et al* concluded anemia is frequent in tuberculosis cases & ACD accounted for 45%(23/51) of anemia among all participants at TB diagnosis. Anemia in TB is mainly due inflammatory cytokines, studies have reported that anemia is a common co morbidity at tuberculosis diagnosis which is partly resolved after TB treatment. Kotwal J *et al* studied 55 HIV infected symptomatic patient. Anemia was present in 45 patients and out of which 66.66% patients had normocytic normochromic anaemia. Iron deficiency anaemia was present in 37.77% patients and anaemia of chronic disease in 62.22% patients. 2 patients had anaemia of the critically ill. Kreuzer KA *et al* quoted microcytosis is rarely observed in HIV infection, while normocytosis appears to be commonly found in these patients.

## CONCLUSION

One of the most important areas for scope in the improvement of health care is prevention of anemia. Anemia of chronic disease is the 2<sup>nd</sup> most common anemia worldwide and the most common anemia in elderly. Anemia of chronic disease is known to be associated with mortality in many disorders. Hence timely diagnosis and effective management is important. Adults being the most vulnerable group for anemia of

chronic disease.

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