Original Article

Inflammatory markers in geriatric anemia: A study from North India

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Abstract

Background: Inflammation has several effects in the geriatrics with reference to iron deficiency anemia (IDA), anemia of chronic disease (ACD), and unexplained anemia (UA). Whether hyperinflammation is part of their pathogenesis or just incidental is unknown. Data are limited regarding inflammatory patterns in IDA, ACD, and UA in anemic geriatrics and inflammation as a component of UA. There is little known about the overlap of inflammation between ACD and UA. **Objective:** The study was undertaken to find the proportion of anemic geriatric patients, aged ≥60 years with raised serum levels of inflammatory markers and their study within IDA, ACD, and UA. **Materials and Methods:** Seventy-five anemic geriatric patients were evaluated for raised serum levels of inflammatory markers: high sensitive C-reactive protein (hsCRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8) along with serum ferritin (SF). **Results:** Raised markers were seen in 94.7% of anemic geriatric patients.IL-8 was raised most frequently followed by TNF-α, IL-6, hsCRP, and SF. No distinct inflammatory profile could be elicited between ACD and UA. The hyperinflammatory profile irrespective of the underlying etiology of geriatric anemia suggests that aging *per se* is pro-inflammatory state. **Conclusion:** Geriatric anemia can be thought to develop on background of subclinical low-grade inflammation along with superimposed nutritional deficiencies or chronic diseases.

Keywords: Geriatric anemia, hsCRP, IL-6, IL-8, inflammatory markers, TNF-α

Introduction

A pro-inflammatory state is commonly seen in geriatrics chiefly because of the high prevalence of chronic noncommunicable diseases that produce inflammation.[1] However, it is also noted in the absence of any such identifiable cause. The evidence for the same is provided by an age-associated increase in serum levels of pro-inflammatory cytokines, namely interleukins (IL-6, IL-8), C-reactive protein (CRP), and Tumor Necrosis Factor (TNF)-α.[2-6] The development of inflammation in geriatric population is attributable to a distinct epigenetic drift, which causes raised serum levels of various proinflammatory cytokines such as IL-1, IL-6, and TNF-α and alters the hematopoietic microenvironment in bone marrow. This altered microenvironment in bone marrow triggers a complex web of pathways involved in the suppression of erythropoiesis by reduced proliferation of precursors, enhanced erythropoietin resistance, faulty iron utilization via increased hepcidin, iron sequestration in macrophages, and intestinal epithelium leading to nonavailability for hematopoiesis, along with a significant reduction in erythroid cell lifespan.[6-8] These underlying pathways are likely more overlapping than identical.[7]

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Anemia is also a commonly encountered condition in geriatrics. With the rising prevalence of anemia in geriatrics, few authors have proposed the consideration of anemia in geriatric population as distinguishable "geriatric syndrome."[9,10] Further, the presence of concurrent inflammation has chiselled out a distinct subset of geriatric anemic patients, wherein the inflammatory response not only is reflective of the acute phase reaction but also hampers the normal hematopoiesis and is closely linked to worsening and precipitation of age-associated disease states including dementia, muscle frailty, sarcopenia, cardiovascular, chronic respiratory disorders and cancer. For instance, there is a strong association of raised CRP levels with anemia.[11] Both geriatric anemia and inflammatory state have similar causes of mortality in geriatrics. Thus, there is a strong relationship between the elevated pro-inflammatory cytokines and the development of geriatric anemia, pointing toward a possibility of potential overlap between the two entities as echoed in a few studies.[7,10] However, our understanding of influence of inflammation on geriatric anemia is so far limited predominantly to anemia of chronic disease (ACD).[6,7,12] Further, it coexists with nutritional anemia, mainly iron deficiency anemia (IDA), and alters the response to hematinics. In unexplained anemia (UA) also, which is present in 1/3rd of geriatric anemics, the role of inflammation is largely unknown.[1-5] Whether inflammation has a causative association in development of anemia through pathways different from those involved in the development of ACD or is it just a coincidental finding is still a matter of debate. Considering these issues, the present study was undertaken to estimate the proportion of anemic geriatric patients with pro-inflammatory states and whether they showed a correlation with the prime etiological categories, that is, IDA, ACD, and UA in geriatric anemia.

Materials and Methods

Study design and setting

It was a cross-sectional descriptive study conducted from November 2016 to March 2018.

Ethical approval

Approval from Institutional Ethics Committee for Human Research (IEC-HR) was obtained.

Study population

All anemic patients aged 60 years and above who visited medicine or geriatric OPDs were enrolled. Hemoglobin (Hb) cut-offs were taken as <12 gm% in females and <13 gm% in males.[5] Patients with hematological malignancies and those who had taken hematinics in the last 10 days or received a blood transfusion in last 1 month were excluded. The tests included a complete hemogram (by Beckman Coulter LH500) with ESR (by Westergren method), reticulocyte count estimation (EDTA tubes), and peripheral smear preparation (by Wright stain). Biochemical tests included iron status [Serum Iron (SI) [by ICSH 1978], Total Iron Binding Capacity (TIBC) [by Resslar and Zak], % Transferrin Saturation (TSAT)], Serum Ferritin (SF) [by ELISA kit. Calbiotech, Inc.], Serum Vitamin $B_{12,}$ and Folate assay [by immunoassay kits. Elecsys].[13,14] Serum levels of inflammatory markers, namely, high sensitivity CRP (hscrp) [by ELISA kit. Bio-Detect USA], IL-6 [by ELISA kit. Diaclone)], IL-8 [by ELISA kit. Diaclone], and TNF-α [by ELISA kit. Krishgen Biosysytems] were also estimated. IDA was diagnosed on the basis of low SI (<60 μg/dL) and SF (<15 μg/L).[15,16] IDA coexisting with ACD was diagnosed when SI was <60 μg/dL and SF was 15 to <30 μg/L.[15] ACD was diagnosed at low SI (<60 μg/dL), low to normal TIBC (N: 250-400 μg/dL), and SF ≥30 μg/L).[15] Vitamin B_{12} deficiency was diagnosed at levels <180 ng/L.[16,17] FA deficiency was diagnosed at levels <3 μg/L.[15-17] Unexplained anemia (UA) was diagnosed when the patients could not be assigned the above-mentioned criteria.[12]

Statistical analysis

Statistical analysis was performed using MS EXCEL and SPSS software. The Chi-square test was applied to check associations between etiology of anemia and comorbidities. Inflammatory parameters had skewed distribution, and Mann-Whitney and Kruskal Wallis tests were applied between IDA, ACD, and UA to check the relationship between their inflammatory parameters. Correlations between inflammatory markers were studied using the Pearson correlation coefficient.

Results

Seventy-five subjects were included in the final study. Their ages varied from 60 to 95 years with mean ± SD of 65.7 ± 6.6 years and median age of 65 years. Seventy-three (97.3%) patients were aged between 60–80 years and only 2 (2.7%) patients were above 80 years of age. The cohort included 32 (42.7%) men and 43 (57.3%) women. Majority (85.3%) of patients were suffering from different illnesses including chronic comorbidities at presentation and anemia was incidentally detected in them. Remaining patients (14.7%) were referred for evaluation of clinical features of anemia in the absence of preexisting comorbidities.

The commonest cause of geriatric anemia was nutritional anemia (35/75, 46.7%) followed by ACD (25/75, 33.3%) and UA (15/75, 20%). Iron deficiency was the most prevalent (22/75, 29.3%) followed by combined deficiency of iron and vitamin B_{12} (7/75, 9.3%) and isolated deficiency of vitamin B_{12} (6/75, 8%). FA estimation could be done in 34 cases only (due to limited assay kits) but none was FA deficient. There were more cases of ACD alone (17/75, 22.7%) than cases of ACD coexisting with IDA (7/75, 9.3%) and vitamin B_{12} deficiency (1/75, 1.3%). In the remaining cases, no explainable cause of anemia was found despite extensive investigations. Hence, these cases were categorized as UA (15/75, 20%) [Table 1]. Twenty percent of patients had more than one cause pointing to multifactorial causation of geriatric anemia. These etiological causes were subsequently consolidated into three main categories of IDA (29 cases), ACD (25 cases), and UA (15 cases) to study the correlation of different inflammatory markers. All cases of

IDA with coexistent ACD were grouped under ACD. Anemia due to vitamin B_{12} deficiency was grouped under category of "Others" (6 cases) and excluded from subsequent analysis. There were no cases with FA deficiency.

The hematologic parameters included a complete hemogram with red cell indices, total leukocyte count (TLC), and platelet count [Table 2]. A statistically significant difference in mean Hb values was found between IDA and ACD (*P* value: 0.006) and between IDA and UA (*P* value: 0.012). However, no statistical difference was noted in Hb values between ACD and UA (*P* value: 0.5). Most (35/75, 46.7%) patients had moderate anemia followed by severe anemia (28/75, 37.3%). Mild anemia was seen in 12/75 (16%) patients (13). Most cases of IDA showed a severe degree of anemia (15/29, 51.7%) followed by moderate (13/29, 44.8%) and mild (1/29, 3.4%) anemia. Anemia in ACD was predominantly of moderate degree (15/25, 60%), followed by severe (7/25, 28%) and mild anemia (3/25, 12%). Mild anemia (7/15, 46.7%) was most prevalent in UA, followed by severe (6/15, 40%) and moderate anemia (2/15, 13.3%). Reticulocyte count ranged from 0–6% with a mean ± SD of 1.0 ± 0.9% indicating that the anemia was hypo-proliferative.

The inflammatory markers included ESR, hsCRP, TNF-α, IL-6, IL-8, and SF. **ESR** was found raised in 68 patients, while **SF** was elevated in 10 patients. **hsCRP** was raised (>6 mg/L) in 31/75 (41.3%) patients. **IL-6** was raised (>2.97 pg/ml) in 38/75 (50.7%) patients. **IL-8** was raised (>29 pg/mL) in 64/75 (85.3%) patients. **TNF-α** was raised (>3 pg/mL) in 49/75 (65.3%) patients. Overall, inflammatory markers were elevated in 71/75 (94.7%) patients [Table 3]. IL-8 was the most frequently raised marker followed by TNF-α, IL-6, hsCRP, and SF.

Table 1: Etiologic spectrum of anemic geriatric patients (*n*=75)

Etiology of Anemia	Number	Percentage
Nutritional Anemia	35	46.7
-IDA	22	29.3
-Combined deficiency anemia (CDA) due to iron and vitamin B_{12} deficiency	7	9.3
-Vitamin B_{12} deficiency	6	8
ACD	25	33.3
-Isolated ACD	17	22.7
-ACD coexisting with IDA	7	9.3
-ACD with Vitamin B_{12} deficiency	1	1.3
UA	15	20
Total	75	100

Table 2: Hematologic profile of anemic geriatric patients (*n*=75)

Parameter	Mean±SD	Range
Hemoglobin (g/dL)	8.6±2.1	2.9-12.5
Hematocrit (%)	24.4±11.5	0.17-47.4
Red cell count ($\times10^{12}$/L)	4.6±5.1	1.5-5.5
Mean Corpuscular Volume (fL)	77.3±13.5	53-120
Mean Corpuscular Hemoglobin (pg)	23.4±5.4	11.6-39.4
Mean Corpuscular Hemoglobin Concentration (g/dL)	29.9±2.1	22.7-36
Total Leukocyte Count ($\times10^{9}$/L)	8.2±3.1	3.1-20.4
Platelet count ($\times10^{9}$/L)	266.7±15.6	11-651
Reticulocyte count (%)	1.0±0.9	0-6

These markers were further raised across IDA, ACD, and UA. SF was raised in 7/25 (28%) patients with ACD (mean: 160.2 ± 209.1, median: 68) and 2/15 (13.3%) patients with UA (men: 126.1 ± 100.4, median: 119) only and reduced in IDA (mean: 7.6 ± 5.5, median: 6). hsCRP was raised in 9/29 (31%) patients with IDA (mean: 4.4 ± 3.7, median: 3.2), 14/25 (56%) patients with ACD (mean: 457.9 ± 2255.8, median: 9.29), and 5/15 (33.3%) patients with UA (mean: 5.3 ± 3.9, median: 4.17). IL-6 was raised in 11/29 (37.9%) of patients with IDA (mean: 12.9 ± 27.4, median: 1), 17/25 (68%) of patients with ACD (mean: 34.9 ± 58.9, median: 7), and 9/15 (60%) of patients with UA (mean: 22.9 ± 53.7, median: 3.4). IL-8 was raised in 24/29 (83%) of patients with IDA (mean: 427.3 ± 567.1, median: 189), 22/25 (88%) patients with ACD (mean: 289.1 ± 417.8, median: 193), and 14/15 (93.3%) patients with UA (mean: 245.8 ± 192.8, median: 213). TNF-α was raised in 21/29 (72.4%) patients with IDA (mean: 94.0 ± 212.1, median: 12.64), 14/25 (56%) patients with ACD (mean: 98.7 ± 214.6, median: 8.51), and 10/15 (66.7%) patients with UA (mean: 48.8 ± 82.6, median: 6.65).

There was a positive correlation between hsCRP and SF (*P* = 0.018). hsCRP (*P* = 0.00) and IL-8 (*P* = 0.003) showed positive correlation with IL-6. TNF-α did not show a significant correlation with any marker. Further, markers were compared between IDA, ACD, and UA and the overall group. SF was statistically different between IDA and ACD (*P* = 0.000) and UA and ACD (*P* = 0.000) as well as in the overall group (*P* = 0.000). hsCRP (*P* = 0.034) and IL-6 (*P* = 0.034) also had statistical significance in IDA as compared to ACD. However, no such difference could be found in the overall group. IL-8 and TNF-α were raised across all categories with no significant difference. None of the raised markers were significantly different between ACD and UA. In UA, hsCRP was found to be elevated in 6/15 (40%) patients. IL-6 levels were elevated in 9/15 (60%) patients. Raised IL-8 levels were found in 14/15 (93.3%) patients. Levels of TNF-α were raised in 10/15 patients (66.7%).

Comorbidities in geriatric anemia

Most patients had associated comorbidities at presentation (43/75, 57.3%). These included diabetes mellitus, hypertension, chronic obstructive pulmonary disease, coronary artery disease etc. Majority (27/43, 62.8%) had more than one comorbid condition while others (16/43, 37.2%) had only one of them. Anemia was incidentally detected in all patients. A large proportion of them had elevated inflammatory markers (40/43, 93%). The most widely raised marker was IL-8 followed by TNF-α, IL-6, and hsCRP [Figure 1]. Interestingly, comorbidities were present in 13/15 (86.7%) patients with UA.

Table 3: Inflammatory parameters in anemic geriatric patients (*n*=75)

	ESR (mm)	SF (g/dL)	IL-8 (pg/mL)	TNF-α (pg/mL)	IL-6 levels (pg/mL)	hsCRP (mg/L)
No. of patients with raised inflammatory markers (%)	68 (90.7%)	10 (13.3%)	64 (85.3%)	49 (65.3%)	38 (50.7%)	31 (41.3%)
Median (Md)	49	25	189	9.2	3	4.2
Range	5–135	2–950	8–2046	1–1082	1–222	0–11.3
Mean	53.9	88.6	327.9	82.2	21.7	5.4
Std. Deviation	29.4	145.2	442.7	184.4	45.5	4.0

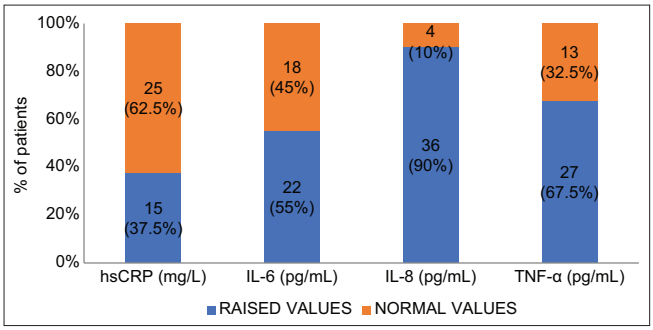

Figure 1: Levels of inflammatory markers in anemic geriatric patients with comorbidities (*N* = 40)

Discussion

Most patients (94.7%) with geriatric anemia showed raised serum levels of one or more inflammatory markers. Amongst those studied, IL-8 was raised in maximum patients (85.3%), followed by TNF-α (65.3%), IL-6 (50.7%), and hsCRP (41.3%). SF was raised in only 13.3% patients. Artz *et al.* mentioned 45% anemic patients with elevated IL-6.[13] Similar elevation in serum levels of pro-inflammatory markers have recently been demonstrated.[14,18,19] However, *IL-8 and TNF-α were not evaluated in those studies.*[14] Higher inflammatory scores (raised CRP, IL-6, IL-1, IL-1β, and TNF-α) and reduced EPO levels have also been found in anemic subjects as compared to non-anaemic subjects by Roy *et al.*[20] The most frequently implicated markers in inducing anemia are IL-6, CRP, TNF-α, and IL-1.[16-20] *However, SF has not been studied as an inflammatory marker in UA in any study.* Role of IL-8 in development of anemia in old is also not properly addressed.[7]

On studying the difference in the pattern of inflammatory markers present in IDA, ACD, and UA, it was noticed that **at least one marker was elevated in 96.6% of patients with IDA and 92% of patients with ACD and all patients with UA (100%)**. SF was statistically different between IDA and ACD (*P* value <0.01) and IDA and UA (*P* value <0.01); it was able to differentiate IDA from both ACD and UA but did not allow differentiation between ACD and UA. *This is the first study to evaluate SF as an inflammatory marker in UA. Presence of raised SF in all UA patients is a novel finding that warrants more research.* hsCRP (*P* value = 0.034) and IL-6 (*P* value = 0.034) were significantly raised in ACD when compared with IDA but could not differentiate between the two. This indicates that **raised hsCRP in UA is not contributing to changes in iron metabolism similar to ACD and different mechanisms may be responsible for its development.** *TNF-α was raised in all diagnostic categories*. It is also noted in 72.4% of patients with IDA. Previous studies found raised TNF-α to be associated with systemic iron deficiency via mechanisms different from those causing ACD.[5,19,20-24] Therefore, elevated TNF-α in IDA in our study as well as in previous studies might be due to a pro-inflammatory state of aging, leading to iron deficiency. Interestingly, *IL-8 was elevated in all categories of anemia.* Artz *et al.* also found raised IL-6, IL-8, and IFN-γ in UA than in non-anemic controls.[13] Few studies emphasize that UA with elevated IL-8 shares features of ACD or anemia of inflammation.[17,25,26] Also, elevated inflammatory markers may be seen in UA when compared with healthy non-anemic controls in the absence of any inflammatory condition.[27] However, it is still not clear if IL-8 induces anemia via mechanisms different from those in ACD and if its presence can explain the currently "Unexplained" anemia.

Association of geriatric anemia with comorbidities was statistically significant (*P* = 0.004). A significant difference was also seen between IDA and UA (*P* = 0.001). Also, 56.4% of patients with raised inflammatory markers had one or more comorbidities, with or without other acute illnesses. This hints at a close relation between inflammatory state produced by chronic comorbidities and geriatric anemia, especially ACD and UA. Comorbidities may have an additive impact on the development and progression of geriatric anemia and may also contribute to UA in the absence of nutritional deficiencies. Due to the chronic and intractable nature of these conditions, anemia is more likely to persist despite therapeutic interventions.[11,28,29] Yet, a significant subset of cases of geriatric anemia possess an inflammatory state "without a chronic inflammatory disorder."

Geriatric individuals with anemia are most likely to consult general practitioners and physicians prior to or without specified diagnostic evaluation at a designated hematology facility. It's a complex age group for the evaluation of anemia for many reasons. Firstly, this subgroup has multiple causes of anemia, which often coexist and overlap. Secondly, there is an increased incidence of lower gastrointestinal bleeding in geriatrics which usually complicates the anemic picture. Thirdly, geriatrics are frequently exposed to polypharmacy and it is tough to segregate the additive effects of multiple medications from the actual cause of anemia.[29] Fourthly, the presentation of anemia in geriatrics is quite different from that encountered in younger individuals. While nutritional anemia presents with more classic manifestations, anemia due to inflammation has vague, non-specific symptomatology, which is likely to be overlooked

as usual signs of aging. There is usually poor reporting of signs and symptoms owing to impaired memory, lack of accompanying attendants and masking of symptoms by other underlying comorbidities.[6,7,10] Despite these physiological differences in causation and presentation of anemia, there are no separate hemoglobin thresholds for defining and characterising geriatric anemia between young adults and geriatrics. It is shown to worsen angina, cerebrovascular disease, cardiovascular dysfunction, and chronic obstructive pulmonary disease.[19] Geriatric anemia has a profound negative impact on survival and overall quality of life, which further varies with inflammation. There is an overall deterioration of physical activities, cognitive decline, depressive affect, and worsening quality of life.[6,30] This subset of patients may remain inadequately treated since they may not benefit from standard hematinic therapy alone and might require additional EPO support.[29]

Hence it is imperative for general practitioners to be aware of the association of inflammation with geriatric anemia and its clinical implications. They are likely to serve as the first and may be the only point of contact for geriatric medical care, advocating the need for prompt identification and evaluation of geriatric anemia. While the complete cure of the underlying chronic inflammatory state may not be feasible, a targeted approach toward symptomatic and supportive care at the primary level can greatly impact the geriatric health care.[11,29]

Strengths of the study

While previous studies have largely focused on the spectrum and pathophysiology of anemia of inflammation in geriatrics, there is a paucity of literature regarding the patterns of inflammation and how they differ across ACD, IDA, or UA in the Indian geriatric population. There is also a lack of published data exploring inflammation as a component of UA in them. Our study results provide valuable insight into behaviour of inflammatory markers and possible patterns of inflammation in geriatric anemia with special reference to ACD and UA in the Indian population.

Limitations of the study

The study had a limited sample size. To validate the above findings larger community-based studies need to be conducted. Moreover, this study is hospital-based, thereby limiting the generalizability of the results. This further presses upon the need for more community-based studies.

Future directions

The data can serve as a stepping stone for further studies on the correlation of inflammatory markers with different etiological forms of geriatric anemia. Larger explorative studies after adjusting for the presence of comorbidities and comparative studies vis-à-vis non-anemic controls may be undertaken.

Summary

Our study identifies that inflammation is an overall common finding in geriatric anaemic patients and identifies IL-8 as the most commonly raised marker present, irrespective of the underlying etiology. Apart from a low SF, no other inflammatory parameter was able to conclusively distinguish between the three main aetiologies. IL-6 and hsCRP were raised in ACD as compared to other causes but the result was not statistically significant, thus limiting its differentiating role as an inflammatory marker.

Take home message

The hyperinflammatory profile of geriatric patients in our study reflects that **aging** per se **is characterised by a pro-inflammatory state**, as shown by high IL-8 and TNF-α levels even in geriatrics with IDA. The presence of widespread inflammation, irrespective of the cause of anemia, suggests a possibility of **other unknown pathways contributing to anemia in geriatrics.** Thus, geriatric anemia can be thought to develop on a **background of subclinical but essential, age-associated low-grade inflammation coupled with superadded effects of nutritional deficiencies or chronic inflammatory diseases. Inflammation should not merely be disregarded as a side effect of common chronic disorders in the geriatric age group.**

Novel findings

To the best of our knowledge, our study is probably the first elaborate study exploring the potential connection between inflammation and geriatric anemia in the Indian population. No other study has specifically taken into account a panel of inflammatory parameters to understand their role in geriatric anemia subcategories with special emphasis on UA. Also, the role of SF as an inflammatory marker in UA has not been studied previously. Specifically, the role of IL-8 as an inflammatory marker has not been addressed and warrants more research.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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