Anemia in the elderly: usefulness of an easy and comprehensive laboratory screen

Anémie du sujet âgé : proposition d’un bilan étiologique biologique systématique

Abstract. Anemia, the most common hematological disorder in the elderly, increases the risk of mortality and morbidity and adversely affects quality of life. However, few studies focused specifically on anemia in the elderly, especially regarding the underlying causes. The main objective of this prospective study was to evaluate the causes of anemia in non-institutionalized elderly patients. We included 190 consecutive patients ≥70 years, admitted to a geriatric short-stay unit over a 1-year period. When the hemoglobin level was <120 g/L, the following serum assays were performed routinely: iron, ferritin, transferrin saturation, folate, vitamin B12, C-reactive protein, TSH, albumin, and haptoglobin. When these tests were normal, bone marrow aspiration was performed to look for myelodysplastic syndrome. Hemoglobin was <120 g/L in 83 (43.7%) of 190 included patients. Patients with anemia had a mean hemoglobin level of 105±11 g/L. The most common potential causes of anemia were inflammation, severe renal impairment, severe malnutrition, and iron deficiency; each of these causes was found in at least one-third of patients with anemia. Myelodysplastic syndrome was found in all anemic patients with a normal serum screen (12/83, 14.5%). Anemia was multifactorial in most patients: the mean number of potential causes per patient was 1.85±1, and 65.4% of the patients had two to four concomitant causes. The serum screen used in our study is easy to perform in ambulatory patients and identifies potential causes of anemia for which safe and effective treatments are available. Second-line bone marrow aspiration adds to the diagnostic yield.

Key words: anemia, elderly, diagnostic testing, myelodysplastic syndrome

Résumé. L’anémie, pathologie hématologique la plus fréquente chez le sujet âgé, est associée à une augmentation de morbi-mortalité et à une diminution de qualité de vie. Cependant, peu d’études s’y sont intéressé, notamment pour l’approche étiologique du diagnostic. L’objectif de cette étude prospective était d’analyser les causes d’anémie chez des patients ≥ 70 ans hospitalisés en court séjour gériatrique sur un an. En cas d’hémoglobine (Hb) < 120 g/L, un bilan biologique complémentaire était systématiquement réalisé : fer sérique, ferritinémie, coefficient de saturation de transferrine, vitamine B12 et folates, CRP, TSH, albuminémie, et haptoglobinémie. Quand ces tests étaient normaux, un myélogramme était réalisé, principalement à la recherche d’une myélodysplasie. L’Hb était < 120 g/L pour 83 (43.7 %) des 190 patients inclus. Les patients anémiques avaient une Hb moyenne à 105 ± 11 g/L. Les causes d’anémie les plus fréquentes étaient l’inflammation, l’insuffisance rénale sévère, la dénutrition sévère et la carence ferrique, chacune étant présente chez au moins 30 % des anémiques. Une myélodysplasie était diagnostiquée chez tous les patients anémiques avec bilan biologique étiologique normal (12/83, 14.5 %). L’anémie était multifactorielle dans la plupart des cas : le nombre moyen de causes par
Anemia is the most common hematological disorder in the elderly. Epidemiological studies consistently showed an increase in the prevalence of anemia with advancing age, despite differences across studies in patient characteristics such as age and co-morbidities [1]. In cohorts of ambulatory patients, about 15% of men and 10% of women over 75 years were anemic; after 85 years of age, the prevalence of anemia increased to 20%-26% in men and 13%-20% in women [1-3]. Prevalences as high as 60% in men and 40% in women have been reported in cohorts of institutionalized patients aged 85 years or over [4-6]. Anemia in the elderly is a public health issue, chiefly because it is associated with increased healthcare costs [7]. Anemia increases the risk of mortality and morbidity and adversely affects quality of life, self-sufficiency, and cognitive functions, thereby increasing the risk of hospitalization [8-13]. Moreover, effective treatment of anemia can result in lower mortality and morbidity rates in the elderly [2]. However, few studies focused specifically on anemia in the elderly, especially regarding the underlying causes [1, 2, 14]. Elderly individuals often have multiple co-morbidities, several of which may contribute to cause anemia [14, 15]. However, advanced age is not a reason for limiting the investigations performed to determine the causes of anemia. Although advanced age is associated with a poor response of the erythropoietic system to stress, it does not cause anemia by itself [16].

Here, our main objective was to determine the prevalence and causes of anemia in very elderly patients. We conducted a prospective cohort study in non-institutionalized patients admitted to a geriatric short-stay unit. The secondary objective was to evaluate whether anemia or the hemoglobin (Hb) level was associated with age, sex, the co-morbidity score, or creatinine clearance.

Methods

The study was approved by the appropriate ethics committee (Comité consultatif de protection des personnes pour la recherche biomédicale – Hôpital Pitié-Salpêtrière).

Patients

Between January and December 2007, consecutive patients admitted to a short-stay unit of a French geriatric teaching hospital were included prospectively in the study if they were aged 70 years or older and were admitted directly from home or after less than 24 hours in an emergency unit. Patients were excluded if they were institutionalized or had a known history of anemia, other hematological disease, or active cancer before admission.

Data collection

For all included patients, we prospectively recorded age, sex, and the 13-item Cumulative illness rating scale in geriatrics (CIRS-G) scores. The total CIRS-G score reflects the overall burden of co-morbidities and the composite CIRS-G score the severity of co-morbidities [17]. The following laboratory tests were performed routinely: complete blood cell counts, serum creatinine, and creatinine clearance (CrCl) determination using the Cockcroft-Gault formula. In patients with anemia, defined as Hb < 120 g/L in both genders, the following serum assays were performed routinely: iron, ferritin, transferrin saturation, folate (also assayed in the erythrocytes), vitamin B12, C-reactive protein, thyroid-stimulating hormone, albumin, and haptoglobin. The following potential causes of anemia were assessed: iron deficiency, folate deficiency, vitamin B12 deficiency, severe renal impairment, inflammation, hypothyroidism or hyperthyroidism, severe malnutrition, and hemolysis. Multifactorial anemia was defined as the presence of more than one of the above-listed causes. When all serum tests for a cause of anemia were normal, bone marrow aspiration was performed.

Statistical analysis

First, we compared patients with and without anemia regarding age, sex, CIRS-G scores (total and composite), and CrCl, using the chi-2 test for sex and the Student t test for the other variables. A univariate analysis was conducted for each parameter. Variables with P values < 0.10 in the univariate analysis were entered into a stepwise logistic regression model. The variables used in the final model were those with P values < 0.05.

Second, we looked for associations between the above-listed variables and the Hb levels in the overall patient population. For the univariate analysis, we used the Mann-Whitney test for sex and Spearman’s correlation coefficient.
for the quantitative variables. The multivariate analysis consisted in multiple linear stepwise logistic regression, using the same thresholds for the final model as those used in the logistic regression. Analyses were performed using SAS, version 8.0 (SAS Institute, Inc., Cary, NC, USA).

Results

Of the 242 patients admitted to the short-stay unit during the study period, 190 were included in the study. There were 123 women and 67 men, with a mean age of 85±7 years (70-103). The mean total CIRS-G score was 9±3.7 and the mean composite CIRS-G score was 3.7±1.5. The mean CrCl was 40.9±16.5 mL/min. The mean Hb level was 122 g/L. The Hb level was <120 g/L in 83 (43.7%) patients and ≥120 g/L in 107 patients. Overall, the prevalence of anemia was 44.7% in women and 41.8% in men. In the group with anemia, the mean Hb level was 105±11 g/L (Table 1). The laboratory screen detected at least one cause of anemia in 71 (85.5%) of the 83 patients. The most common causes of anemia were inflammation, severe renal impairment (CrCl <30 mL/min), severe malnutrition (serum albumin <30 g/L), and iron deficiency, with each of these causes being found in at least one-third of patients with anemia (Figure 1). The 12 patients with anemia but normal laboratory screen findings (12/83, 14.5%) underwent bone marrow aspiration, which consistently showed myelodysplastic syndrome (MDS): refractory anemia in 1 patient, refractory cytopenia with multilineage dysplasia in 9 patients, and type 1 refractory anemia with excess of blasts in 2 patients. In patients with anemia, the mean number of causes of anemia per patient was 1.85±1.02 (0-4), and 65.4% of patients had two to four concomitant causes. When we compared age, sex, CrCl and co-morbidity scores in the groups with and without anemia, we found that the total CIRS-G score was the only variable significantly and independently associated with anemia (P<0.001) (Table 1).

The total CIRS-G score was also the only variable associated with the Hb level in the multivariate analysis on the overall cohort of 190 patients (P<0.001).

Discussion

Here, we evaluated potential causes of anemia in very elderly patients with substantial co-morbidities as indicated by the CIRS-G scores. The original feature of this study is the routine use in anemic patients of a comprehensive laboratory screen, with bone marrow aspiration when the screen was normal. The results confirm that anemia is often multifactorial in the elderly [9]: 65% of anemic patients had two to four concomitant potential causes of anemia. The main data on causes of anemia in the elderly come from the Third national health and nutrition examination survey (NHANES III), an epidemiological study including 1822 ambulatory patients with anemia, mean aged 75 years [2]. It was conducted in the United States and primarily evaluated vitamin and iron deficiencies, which were found in 34.5% of patients. Similarly, nutritional deficiencies were major causes of anemia in our study. Their high prevalence supports routine screening of elderly patients for anemia, particularly as simple and effective treatments are available in most cases [18]. In NHANES III, patients without nutritional deficiencies were investigated for renal failure and/or inflammation, which were found in 32% of cases. In our cohort, the incidence of inflammation was higher, probably because we included both acute and chronic inflammation. Both types may cause anemia, mainly via erythropoiesis inhibition by cytokines, although the mechanisms of inflammatory anemia are incompletely elucidated [19]. Severe renal impairment was found in nearly one-third of our patients and was a possible cause of anemia in almost half the anemic patients. Renal failure must be looked for routinely as a cause of anemia in the elderly, both because renal failure is common after 80 years of age and because recombinant erythropoietin is simple and effective, albeit...
underused [20]. Protein malnutrition is usually not considered a cause of anemia per se and its role is difficult to evaluate, because malnutrition is often associated with vitamin deficiencies and co-morbidities that can contribute to anemia. Some proteins are essential for blood cell production, and protein deficiency may contribute directly to the development of anemia.

Our investigation strategy detected at least one potential cause of anemia in all 83 patients. Conversely, in earlier cohort studies of elderly patients, anemia remained unexplained in 16% to 43% of cases [2, 4, 21, 22]. This difference may be explained by the comprehensive nature of the laboratory screen performed in all our anemic patients and by our policy of performing bone marrow aspiration in all patients with anemia but normal laboratory screen results. Bone marrow aspiration showed MDS in all 12 of these patients. The true prevalence of MDS in elderly patients with anemia may be even higher than the 14.5% prevalence, as we excluded patients with known hematological disorders. In NHANES III, the cause of anemia remained unidentified in 34% of cases, but bone marrow aspiration was not performed and 17% of patients had additional blood count abnormalities suggestive of MDS [2]. Diagnosing MDS is useful in elderly patients with anemia, both to assist in establishing the prognosis and to allow appropriate treatment, most notably with recombinant erythropoietin [23].

We found a significant association between anemia, the Hb level, and the total CIRS-G score. Anemia may be associated with a higher total CIRS-G score, since it adversely impacts co-morbidities. The association with the CIRS-G score supports the usefulness of this score as a marker for frailty, whose pathogenic factors include several causes of anemia (mainly nutritional deficiencies and chronic diseases).

Our study has several limitations. In keeping with other studies assessing the causes of anemia in different settings, we identified potential causes in elderly patients, but we did not evaluate causality. Only follow-up and interventional studies allow an assessment of causality. We defined anemia as Hb < 120 g/L in both genders. The relevance of the WHO definition (Hb < 130 g/L in men and < 120 g/L in women) in elderly patients has been challenged [1, 14, 24-27]. Several longitudinal studies showed that the mean Hb level decreased after 70 years of age, especially in men, due to a decline in the levels of the erythropoiesis-stimulating hormone testosterone [28]. Thus, in the elderly, the 120 g/L cut-off seems appropriate for both men and women.

In conclusion, the peripheral-blood laboratory screen used in our study is easy to implement in ambulatory clinical practice. Bone marrow aspiration should be performed as a second-line investigation in patients whose screen is normal. The results of our study highlight the high prevalence of several potential causes of anemia in geriatric patients, most notably renal failure, myelodysplastic syndromes, and nutritional deficiencies. They also confirm the multifactorial nature of anemia in the elderly, which raises challenges for designing interventional studies. However, such studies are needed to confirm the causal link between anemia and laboratory test abnormalities [8]. Studies are also needed to define the optimal hemoglobin levels for health and to evaluate therapeutic interventions.

Conflicts of interest: none.

References
Biological screening of anemia in the elderly