Determinants of anaemia in the very elderly: a major contribution from impaired renal function?

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Background. Anaemia in the very elderly is usually dissected to a variety of root causes. The frequency of nutritional anaemias is particularly uncertain, since there is controversy on the real prevalence of folate, vitamin B12 and iron deficiencies, as well as on their potential pathophysiological relationship with anaemia.

Materials and methods. We retrospectively analysed results of haemoglobin, ferritin, folate and vitamin B12 measurements performed on a cohort of unselected subjects over 85 years old who were referred by general practitioners for routine diagnostic check-up to our laboratory over the past 2 years. Furthermore, glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) formula.

Results. The overall prevalence of nutritional deficiencies was low in males (<25%) and very low in females (<15%). Significant differences between anaemic and non-anaemic subjects were observed only for GFR in both males (44±3 versus 67±3 mL/min/1.73m^2; p=0.035) and females (42±3 versus 61±3 mL/min/1.73m^2; p=0.019). Likewise, a significantly difference in the frequency of anaemic and non-anaemic subjects with values below the conventional thresholds of the parameters tested was observed only for GFR in both males (59 versus 14%; p<0.001) and females (61 versus 41%; p<0.001), and for ferritin in females (15 versus 5%; p<0.001). In multiple linear regression analysis haemoglobin values were significantly associated only with GFR (both in men and women).

Discussion and conclusion. The results of this study suggest that impaired renal function might be the major determinant of anaemia in the very elderly. Accordingly, the cost-effectiveness of screening for nutritional deficiencies in older individuals is doubtful, since it would be associated with substantial expenditure and limited diagnostic efficiency.

Key Words: anaemia, elderly, ferritin, folate, renal function, vitamin B12.

Introduction

More than 10% of community-dwelling adults aged over 65 years old fulfil the World Health Organisation (WHO) criteria for anaemia (haemoglobin concentration <120 g/L in women and <130 g/L in men). After the age of 50 years, the prevalence of anaemia increases substantially with advancing age, exceeding 20% in subjects aged 85 years and older[1]. Anaemia is an independent predictor of poor outcomes with many diseases, especially in the elderly, and is predominantly associated with changes in quality of life, decreased cognition and

functional ability, and increased risk of falls, infections, morbidity, and mortality[2]. Therefore, recognising and correcting the underlying cause of the anaemia is an important aspect in the care of the elderly patient[3].

Unlike in younger adults, anaemia in the elderly is not often readily apparent, nor attributable to a single cause, since it can be generally dissected to a variety of root causes including renal insufficiency, inflammation, testosterone deficiency, stem cell proliferative decline and nutritional deficiencies[4]. Nutritional anaemias are of particular clinical interest, because they can be easily reversed and their underlying causes, most often unrelated to dietary intake, require personalised assessment[5]. The prevalence of nutritional anaemias in the elderly, which are not always distinguished from non-anaemic deficiency, is however uncertain. In particular, controversy exists on the prevalence of folate, vitamin B12 and iron deficiencies, as well as on their potential pathophysiological relationship with anaemia. Some lines of evidence suggest that approximately one third of older adults with anaemia might have iron, folate, and/or vitamin B12 deficiency[1], nearly two thirds being associated with iron deficiency due to chronic blood loss from gastrointestinal lesions. The remaining cases are usually associated with vitamin B12, most frequently related to food-cobalamin malabsorption, and/or folate deficiency[6]. Regardless of these data, however, other studies failed to identify a significant association between nutritional deficiencies and haemoglobin values[3,7,8], so that there are no definitive recommendations on investigating iron, vitamin B12 and folate metabolism to prevent anaemia in very elderly individuals, or on correcting nutritional deficiencies[7].

Since appropriate diagnosis and management strategies of anaemia in the elderly, especially in the very elderly, are important aspects for preventing adverse outcomes, we performed an epidemiological investigation to assess the prevalence of nutritional deficiencies and potential causes of anaemia in older outpatients.

Materials and methods

We retrospectively analysed results of haemoglobin, serum creatinine, ferritin, folate and vitamin B12 measurements performed on a cohort of unselected subjects over 85 years old who were referred by general practitioners for routine diagnostic check-ups to our laboratory over the past 2 years. Venous blood samples from outpatients were routinely collected in the morning after an overnight fast. Haematological testing was performed on an ADVIA 120 (Bayer Diagnostics, Newbury, Berkshire, UK). Serum folate and vitamin B12 were assayed using an Immulite 2000 immunoassay system (Diagnostic Products Corporation, Los Angeles, CA, USA), whereas serum ferritin was analysed using a Liaison instrument (DiaSorin, Milan, Italy). The total imprecision of the folate immunoassay is in the range between 3.8-6.2%, whereas that of the vitamin B12 immunoassay is between 3.1-10.3%[9]. The within-run and between-run imprecision of the ferritin assay are <3% and <5%, respectively[10]. Serum creatinine was measured on a Roche/Hitachi Modular System P (Roche Diagnostics GmbH, Mannheim, Germany) by a creatinine Jaffe, rate blanked and compensated assay. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) formula, as modified by Levey *et al*.[11] for methods traceable to the serum creatinine reference system: GFR = 175 x (serum creatinine$^{-1.154}$) x (age$^{-0.203}$) x 1.212 (if black) x 0.742 if female. Throughout the study the quality of results was validated by regular internal quality control procedures and participation in an external quality assessment scheme.

The lower limit of the reference range for GFR calculated according to the MDRD formula is <60 mL/min/1.73 m^2. Based on the larger Scripps-Kaiser database, anaemia was defined as a haemoglobin concentration <13.2 dg/L in older men and <12.2 dg/L in older women, respectively[12]. Low serum levels of folic acid, vitamin B12 and ferritin were established at <7.0 nmol/L, <125 pmol/L[13] and <20 ng/mL, respectively.

The statistical significances of differences and frequency distribution of values were assessed by the Mann-Whitney test (for continuous variables) and the chi-squared test (for categorical variables), respectively. The association between haemoglobin and other variables was tested by multiple linear regression analysis. Statistical analyses were performed using the statistical package SPSS-version 12 and results are presented as the geometric mean and standard error of the mean (SEM).

Results

Cumulative results were retrieved from the database of our Laboratory Information System for 604 elderly outpatients (252 males and 352 females, age range: 85-101 years). Among these, 204 males (81%) and 270 females (77%) had haemoglobin values below the gender-specific thresholds for anaemia. The results of the present investigation are shown in table I. The overall prevalence of nutritional deficiencies was low in males (from 11 to 25%) and very low in females (from 5 to 15%), folate deficiency being the most prevalent abnormality in males (from 21 to 25%) and iron deficiency the most prevalent in females (from 5 to 15%). After clustering the study population according to the gender-specific haemoglobin thresholds, significant differences between anaemic and non-anaemic subjects were observed only for the GFR in both males (44±3 versus 67±3 mL/min/1.73 m^2; p=0.035) and females (42±3 versus 61±3 mL/min/1.73 m^2; p=0.019). Likewise, a statistically significant difference in the frequency of anaemic and non-anaemic subjects with values below the conventional thresholds of the parameters tested was observed only for GFR in both males (59 versus 14%; p<0.001) and females (61 versus 41%; p<0.001), and for ferritin in females (15 versus 5%; p<0.001) (Table I).

In multiple linear regression analysis haemoglobin values were significantly associated with GFR in both men (standardised beta coefficient: -0.158, p=0.038) and women (standardised beta coefficient: -0.169, p=0.026), but not with ferritin (men: standardised beta coefficient: 0.138, p=0.134; women: standardised beta coefficient: 0.117, p=0.123), vitamin B12 (men: standardised beta coefficient: 0.074, p=0.416; women: standardised beta coefficient: -0.090; p=0.235) or folate (men: standardised beta coefficient: -0.092, p=0.331; women: standardised beta coefficient: 0.040; p=0.591).

Table I - Results of haematological testing, serum ferritin, folate, vitamin B12 and glomerular filtration rate clustered according to anaemia thresholds in both genders. The statistical significances of differences and frequency distribution of values were assessed by the Mann-Whitney test (for continuous variables) and the chi-squared test (for categorical variables), respectively

	Males		*P*	Females		*P*
	Haemoglobin <13.2 dg/L	Haemoglobin >13.2 dg/L		Haemoglobin <12.2 dg/L	Haemoglobin >12.2 dg/L	
Number	204	48		270	82	
Age (years)						
Mean ± SEM	82±1	80±1	0.058	84±1	83±1	0.059
MCV (fL)						
Mean ± SEM	90±1	94±1	0.080	88±1	91±1	0.065
RDW (%)						
Mean ± SEM	15.8±0.3	13.9±0.3	<0.01	15.8±0.2	13.6±0.2	<0.01
Ferritin (ng/mL)						
Mean ± SEM	147±25	101±45	0.065	93±23	101±21	0.104
<20 (%)	22 (11%)	4 (8%)	0.375	40 (15%)	4 (5%)	<0.01
Folate (nmol/L)						
Mean ± SEM	13.0±4.5	15.6±11.2	0.307	14.9±3.7	15.8±3.0	0.188
<7 (%)	52 (25%)	10 (21%)	0.252	38 (14%)	8 (10%)	0.146
Vitamin B12 (pmol/L)						
Mean and SEM	289±64	232±67	0.184	288±57	359±137	0.073
< 125 (%)	32 (16%)	10 (21%)	0.205	36 (13%)	8 (10%)	0.228
GFR (mL/min/1.73 m^2)						
Mean ± SEM	44±3	67±3	0.035	42±3	61±3	0.019
<60 (%)	120 (59%)	14 (29%)	<0.01	164 (61%)	34 (41%)	<0.01

GFR = glomerular filtration rate, RDW = red blood cell distribution width, MCV = mean corpuscular volume; SEM = standard error of the mean.

Discussion

A high prevalence of biochemical evidence of vitamin B12, folate or iron deficiency has been reported in a number of areas in the world. However, the indication that these biochemical abnormalities are associated with a comparable prevalence of anaemia is a matter of debate, especially with regards to the elderly[3]. The results of our investigation might thereby have some significant clinical implications. First, in our cohort of unselected consecutive very old outpatients the frequency of anaemia was unexpectedly high, much higher than that previously reported, being 77% in women and 81% in males, respectively. Then, by demonstrating that impaired renal function might be a major determinant of anaemia in the elderly, we have further highlighted the importance of a virtual pathophysiological loop in the elderly, linking anaemia and impaired renal function[14], even though we could not rule out functional iron deficiency, namely anaemia of chronic disease, in some of these patients. According to this mutual relationship, not only might measurement of haemoglobin be useful in patients with impaired renal function to identify those with a higher risk of having or developing anaemia, but also assessment of renal function, using a simple and reliable formula such as the MDRD one[11], might be worthwhile in very elderly anaemic patients for the early identification of renal disease. In fact, it is widely acknowledged that the prevalence of both renal insufficiency and anaemia increase with ageing, since some of the changes in renal function can be traced to age-related alterations in the renal vasculature that may dissociate renal blood flow from glomerular filtration[14]. Although there is a paradoxical feedback in renal production of erythropoietin, since the levels of this hormone actually increase over time, it has also been reported that the erythroid marrow may become less sensitive to erythropoietin stimulation, a key factor contributing along with possible nutritional deficits and co-morbidities to the development of anaemia in the elderly[3]. Since elderly patients can be classified into those with "normal" renal function (GFR ~75 mL/min/1.73 m^2), in whom serum erythropoietin levels are modestly increased, and into those affected by kidney diseases (GFR < 75 mL/min/1.73 m^2), in whom serum erythropoietin levels are reduced, it is possible that a discrete number of renal patients could have been included in our study population, given the low mean value of GFR. This finding has a practical implication, in that erythropoietin administration might be considered in non-complicated renal patients to correct anaemia. Although screening for deficiencies in vitamin B12 and folate is commonly advocated to prevent anaemia in very elderly individuals, a second crucial issue highlighted in this study is the overall low prevalence of nutritional deficiencies in older individuals, always <25% (Table I). We also demonstrated a low predictive value of folate, B12 and ferritin testing for identifying anaemia, so that the cost-effectiveness of performing these tests would be doubtful, resulting in substantial expenditure associated with a very limited diagnostic efficiency, at least in our population of very elderly individuals. This hypothesis is further supported by the evidence that a substantial number of older patients have unexplained anaemia[7], and a high frequency of biochemical evidence of vitamin B12 or folate deficiency does not translate into a comparable prevalence of anaemia[3]. The limited increase in the prevalence of very elderly females subjects with iron deficiency does, however, raise the question of whether assessing iron status in anaemic female patients might be worthwhile[15]. Nevertheless, given the association of anaemia with poorer quality of life and increased mortality, it is still advisable to evaluate each anaemic patient carefully, irrespective of the screening costs, provided that the diagnostic tests chosen are appropriate, reasonable and justified.

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