



Prevalence and causes of Anaemia in Children: A Hospital-Based Diagnostic Study

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Abstract

Anaemia in children is a major public health problem throughout the world. It is estimated that at least one-third of the population has been at one-time anemic. It is often multifactorial, iron deficiency being the most frequent etiology and reasons like malaria endemicity, poor nutrition including micronutrient deficiency, haemoglobinopathies, frequent bacterial infections and high parasitic infestations have been given for these high prevalence rates. The ranges for Hb were first derived from 554 subjects in whom laboratory values for serum iron/iron-binding capacity, mean corpuscular volume, and erythrocyte protoporphyrin were all normal ($\geq 16\%$, ≥ 80 fl, and ≤ 75 $\mu\text{g/dl}$ red blood cells, respectively). Using these reference standards, the prevalence of Anaemia (Hb values below the 95% reference range for age and sex) among the 354 subjects with complete laboratory results was highest in infants (5.8%), teenage girls (5.10%), young women (5.9%), and elderly men (4.5%). Chronic Anaemia may impair growth, cardiac function and cognitive development in infants but other consequences are rather poorly explored more thoroughly. Chronic disorders and iron deficiency were the most common causes of Anaemia. Anaemia was frequently diagnosed in this series of elderly patients. Partly treatable nutritional deficiencies, such as iron or folate deficiency, were identified as possible causes. A complex and heterogeneous interplay of chronic inflammation, functional iron deficiency, and renal impairment was identified in a large proportion of patients. Measures directed at prevention and control of anemia, include increased coverage of supplementation and fortification programs are strongly recommended.

Keywords: Anaemia, iron-deficiency hemoglobin, prevalence of Anaemia, hemoglobin.

Introduction

National Health and Nutrition Examination Survey (NHANES II) provide adequate data on which to base estimates of the prevalence of iron-deficiency Anaemia and the Anaemia of inflammatory disease (Mozaffarian et al. 2015).

An edited data tape for the laboratory analyses that are relevant to iron deficiency (Bothwell et al., 1979; Dallman et al., 1980). Values for serum ferritin on a subpopulation of 157 subjects were used in certain of the analyses. The prevalence of Anaemia is usually defined in terms of the

percentage of individuals with Hb values below a 95% reference range (Osei-Bimpong et al., 2012; Hong et al., 2012). 95% reference ranges for Hb concentration was taken from NHANES II because this large and carefully conducted survey offered the prospects of providing a stronger basis for reference values than previously available. For this purpose, we included only those subjects who provided venous blood samples and excluded all subjects with pregnancy, hemoglobinopathies, or an abnormality in iron/total iron-binding capacity (Fe/TIBC), mean corpuscular Hb (MCV), or erythrocyte protoporphyrin (EP). These reference ranges were then used as a basis for estimates of the prevalence of Anaemia, ie, the percentage of individuals with Hb values below the 95% reference range for age and sex.

Anaemia can also be considered in terms of the *depression* of Hb concentration by the presence of common abnormalities such as iron deficiency or inflammatory disease (in which laboratory abnormalities are similar), even if that depression occurs within the “normal” reference range. The relative prevalence of Anaemia defined in this manner was estimated from the degree to which the frequency distribution for Hb concentration shifted toward higher values after exclusion of subjects who had one or more laboratory values indicative of iron deficiency and/or inflammatory disease. Anaemia is a common problem in elderly patients that usually develops gradually, allowing the body to adapt. Its effects can be life threatening, particularly as part of various co-morbidities in geriatric patients, and it is therefore a difficult diagnostic and therapeutic dilemma for medical practitioners (Merono et al., 2012; Pasricha et al., 2010). Anaemia is an important sign of disease and an evaluation is almost always warranted to determine the underlying cause. It has been shown that Anaemia defined according to the WHO criteria (hemoglobin level ≤ 13 g/dl in men and ≤ 12 g/dl in women) is associated with increased mortality in elderly community residents (Moura, 2015). Imbalanced production and removal ratio results in Anaemia, which may

be acute and rapidly life threatening or chronic. Children are especially at risk of Anaemia: iron deficiency is the most frequent cause at this age because of the disequilibrium between rapid growth and insufficient iron intakes (Wang et al., 2013; Laxmaiah et al., 2007).

Signs and symptoms of Anaemia

When Anaemia is present insidiously, such as with iron deficiency, the diagnosis is often delayed. Cutaneous pallor is not helpful because of the wide variability in skin pigmentation depending on ethnic origin. Conversely, conjunctival pallor, tongue pallor, and pallor of palms and soles seem to be more reliable (Chalco et al., 2005; Kalantri et al., 2010). Reduced food intake and fatigue may be frequent (Teunissen et al., 2014; Panepinto et al., 2014). The degree of tachycardia is correlated with the Hb level and reflects the tolerance of Anaemia (Gv et al., 2014). Signs of hemolysis may be present, such as jaundice or dark urine. Dysmorphic features may help to diagnose a thalassemic syndrome (frontal bossing, prominent malar eminence, and depressed bridge of the nose).

Vitamin B12 deficiency Anaemia was diagnosed if the serum vitamin B12 level was low (less than 211 ng/l), associated with macrocytosis (mean corpuscular hemoglobin > 98 fl). Folate deficiency Anaemia was diagnosed if the erythrocyte folate level was low (less than 186 μ g/l) combined with macrocytosis. The diagnosis of hematological malignant conditions was based on examinations of the bone marrow aspirate and biopsy. Renal disease was accepted as the cause of Anaemia if the patient was known to have chronic renal failure, or had small kidneys on ultrasound examination and the results of the iron studies, serum vitamin B12 levels and erythrocyte folate levels were normal (Wonke et al., 1998). Dietary iron intake Overall, women do not make major changes in their dietary habits during pregnancy (Trygg et al., 1995; Pedersen et al., 2003), which means that the results of nutrition surveys in non-pregnant women can be transferred to pregnant and postpartum women. Danish women of

reproductive age have a mean dietary iron intake of ~9 mg/day (Pedersen et al., 2003), which means that more than 90% of the women have an intake below the recommended daily allowance of ~18 mg/day (NCM, 2004). 96% of the women had a dietary iron intake below the recommended 18 mg/day (Trygg et al. 1995; NCM, 2004). In the third trimester, there is too short time for oral iron treatment to be effective in the correction of Anaemia due to the limited iron absorption capacity. Gastrointestinal iron absorption is regulated according to body iron reserves and the intensity of erythropoiesis. Exhausted body iron reserves in otherwise healthy women will increase the intestinal iron absorption (Krafft and Breymann 2011). In women who do not respond to oral iron, i.v. iron therapy should be considered. The recently introduced third-generation i.v. iron compounds are ferric iron carboxymaltose (Ferinject; Vifor Pharma Ltd.) (Ferinject, 2011; Lyseng-Williamson and Keating, 2009) and ferric iron isomaltoside 1000 (Monofer Pharmacosmos Ltd. 2011).

Material and Methods

The study was conducted in VIMS and their associated hospital Gajrola (Uttar Pradesh) India from 2014 to 2016. The sample design certain subgroups in the population that were of special interest for nutritional assessment were oversampled: preschool children (6 months through 5 yr old), persons 62 through 75 yr old, and the poor (persons living in local areas). For the purposes of this report, we excluded 57 subjects from the latter group because of pregnancy (n = 20), abnormal Hb electrophoresis (n = 35: primarily Hb AS, 15; AC, 10; elevated F, 5; and elevated A2, 5), or because only skin puncture blood could be obtained (n=2). These exclusions involved primarily young women (pregnancy), hemoglobinopathies, and children under the age of 5 yr (skin puncture blood). The remaining group of subjects was the basis for (Table. 1 and Table. 2.) was based on those of the subjects who had normal values for Fe/TIBC,

MCV, and EP by criteria that will be described below. Although (Table. 1 and Table. 2.) show actual numbers of subjects, the laboratory findings for each person in the sample were inflated by the reciprocal of selection probabilities, adjusted to account for persons who were not examined, and stratified afterward according to race, sex, and age, so that the final.

Laboratory Analysis and Definition of Anaemia

Anaemia was defined according to World Health Organization criteria as Hemoglobin (Hb) <120 g/l in women and <130 g/l in men (WHO, UNICEF, UNU 2001; FAO, WHO, 1992). Its severity was graded as mild when Hb was 100-129 g/l in men and 100-119 g/l in women, and either moderate or severe when Hb was 70-99 g/l and less than 70 g/l, respectively in women. In men, it was graded either moderate or severe when Hb was 80-109 g/l and less than 80 g/l, respectively (WHO, UNICEF, UNU 2001; FAO, WHO, 1992). Anaemic status, severity and its possible causes were identified from admission blood samples with hematinic parameters like serum ferritin, vitamin B12 and folate levels in most of the patients. In patients with normal hematinic parameters relevant additional tests were done to evaluate the etiology. Anaemia was classified as normocytic if Mean Corpuscular Volume (MCV) was 83-101 fl (Osei-Bimpong et al., 2012). Any value above this was considered as macrocytic and any value below this as microcytic. Automated cell counter (Coulter LH-500, Beckman Coulter) was used to measure haemoglobin and red cell indices on admission.

Definition of Anaemia and nutritional deficiencies

Absolute iron deficiency was defined as a serum ferritin <30 ng/mL. Functional iron deficiency was subcategorized as mild or moderate based on transferrin saturation <16% and serum ferritin >100 ng/mL or serum ferritin 30-100 ng/mL, respectively (Ludwig et al., 2013; Aapro et al., 2012). Moreover, Anaemia was classified as microcytic (<77 fl) and normocytic (77-96 fl).

Factor associated to Anaemia are Genetic haemoglobin disorder, Nutrition and infectious disease factor (Fig.1).

Estimation of relative prevalence of a depression in Hb concentration iron deficiency and inflammatory disease

We estimated the relative prevalence of depressed Hb values due to iron deficiency or inflammatory disease by determining the shift in the median Hb concentration. Using the 50th percentile to calculate relative prevalence has the advantage of including individuals in the lower half of the Hb (or hematocrit) distribution, where overlap between normal values and those influenced by iron deficiency is greatest (Garby et al., 1969). We performed these calculations by using the criteria described above. We use the term, relative prevalence to indicate that the values are merely estimates and that they are most useful in comparing prevalence according to age and sex. An example of the calculation of relative prevalence is as follows: in women between 25 and 34 yr of age, the 50th percentile for Hb concentration shifted from 13.29 to 13.41 g/dl after excluding individuals on the basis of the above mentioned laboratory criteria. The new value of 13.41 g/dl now corresponded to the 54.6th percentile of the original unscreened group, representing a shift of 4.6 percentiles or a relative prevalence of 4.6%. We intentionally focused on iron deficiency in terms of its effects on Hb concentration since there is little convincing evidence that depletion of storage iron has adverse health consequences if the Hb concentration has not been affected (Dallman, 1982). Furthermore, the borderline between depletion of storage iron and the normally marginal state of iron stores in infants, children and young women may be arbitrary or difficult to define.

Statistical analyses

Reference ranges were derived only from groups in which the sample size exceeded 30, based on an extrapolation from a recent report in which the minimum numbers for which reliable estimates of

the 5th and 95th percentiles could be obtained was listed as 100 and the corresponding number for the 10th and 90th per centiles was 50 (Hong et al., 2012). Mean values for serum ferritin were calculated after logarithmic transformation because the values approach a log-normal distribution. The significance of differences between means was estimated by "Student's" t test. The estimation of 95% confidence limits for relative prevalence of a depression in Hb concentration was based on the fact that mean and median values for Hb were virtually identical. We therefore assumed that the 95% range around the median Hb values in the screened population was equivalent in magnitude to the ± 2 SE range around the mean. The 95% range in relative prevalence was then derived from the Hb percentiles of the original, unscreened group that corresponded to the assumed 95% confidence limits around the median Hb in the screened population.

Results

The developmental increase in values during childhood and the further rise in concentrations during adolescence in the male are in general accord with previously published values (Bothwell et al., 1979; Dallman et al., 1980). With increasing age in the adult, there was a slight rise in concentration of Hb in women and a substantial decline in men. The 95% range broadened in the elderly of both sexes but particularly in men. For the purposes of this report, the values listed for all races will be considered as reference values. The values for all races and for whites were very similar; Blacks accounted for only 12% of the total weighted population. However, in accordance with previous studies (Meyers et al., 1979), there was a lower median Hb concentration in Blacks than in whites that varied from 0.4 g/dl in children between 3 and 5 yr of age to 1.1 g/dl in men between 65 and 74 yr of age. The possible reasons for the difference in concentration of Hb and the extent to which it is due to genetic, socioeconomic, or dietary factors are important

and complex issues but ones that requires more detailed analysis than is possible in this report. The basis for the discrepancy is unclear, but it does not appear to be attributable to a difference in prevalence of iron deficiency.

Prevalence of Anaemia: percentage of values below the 95% reference range

The percentage of individuals with Hb values below the reference range is shown according to age and sex on Table 1. The pattern of laboratory abnormalities of anemic subjects in those groups with a high relative prevalence of Anemia suggested differences in the predominant etiology of the Anaemia. Mean values for several laboratory tests in infants between 1 and 2 yr old, in women 25 to 44 and men 65 to 75 yr of age are shown in Table 2. For each of these groups, laboratory values are shown for those whose concentration of Hb was in the anemic range compared to those with a Hb concentration above the lower limit of the reference range for age and sex (Table 2). In infants, young women, and elderly men, those who were anemic had lower Fe and Fe/TIBC, and higher EP values than the remaining group; the MCV was significantly depressed in the infants and young women but not

in the elderly men. From these results alone, it was difficult to distinguish between iron deficiency and inflammatory disease as a major basis for Anaemia in each group (Bothwell et al., 1979; Dallman et al., 1980). However, the results of the TIBC and serum ferritin gave some indication of the relative contribution of the two conditions. TIBC is often depressed in individuals with inflammatory disease, infection, or protein deficiency, whereas it is elevated in many individuals with iron deficiency (Bothwell et al., 1979; Dallman et al., 1980). Serum ferritin is depressed in iron deficiency but typically elevated in inflammatory disease (Bothwell et al., 1979; Dallman et al., 1980). The mean TIBC was significantly elevated ($p < 0.01$) in anemic infants and young women but not in the anemic elderly men. The serum ferritin was depressed in the anemic young women ($p < 0.01$) but not in the elderly men with Anaemia (no serum ferritin analyses were done in children under 3 yr old). These results indicate that iron deficiency was predominant as a cause of Anaemia in the infants and young women but that Anaemia seemed more commonly related to inflammatory disease and perhaps other conditions in elderly men.

Table 1 Prevalence of Anaemia: percentage of values below the 95% reference range

| Age (Yr) | 1-2 | 3-5 | 6-8 | 9-11 | 12-14 | 15-17 | 18-24 | 25-44 | 45-64 | 65-75 |
|-----------------|-----|-----|-----|------|-------|-------|-------|-------|-------|-------|
| Male and Female | 5.7 | 3.5 | 2.3 | 2.8 | | | | | | |
| Males | | | | | 2.9 | 2.9 | 2.9 | 2.9 | 3.8 | 4.4 |
| Female | | | | | 3. | 5.9 | 5.9 | 5.8 | 3.9 | 3.9 |

Table 2. Laboratory characteristics of anemic and non-anemic subjects (n=354) (value below the 95%)

| | Group: age (Yr) | N | Fe* µg/gl | TIBC µg/gl | Fe/TIBC % | MCV fl | EP* µg/gl red blood cells | Ferritin n µg/gl | |
|----------|-----------------|-----|--------------|---------------|--------------|-----------|---------------------------------|------------------------|------|
| Infants: | 1-2 Anemic | 3 | 57.8 | 445 | 13.0 | 74.9 | 126.1 | | |
| | Non anemic | 46 | 81.3 | 408 | 20.2 | 78.6 | 67.3 | | |
| Women | 25-44 Anemic | 40 | 78.8 | 392 | 20.4 | 87.5 | 71.6 | 66 | 14.9 |
| | Non anemic | 180 | 99.8 | 375 | 27.1 | 90.2 | 54.4 | 471 | 29.0 |
| Men | 65-75 Anemic | 25 | 89.9 | 355 | 25.4 | 91.1 | 79.4 | 50 | 90.9 |
| | Non anemic | 50 | 102.2 | 348 | 29.5 | 91.0 | 51.2 | 296 | 93.8 |

To convert to international system of units (SI), multiply Fe and TIBC values by 0.179 to obtain mol/l and multiply EP values by 10 to obtain µg/l red blood cells.

[†]Anemic group differs from non-anemic, $p < 0.01$; all other differences are not significant, $p < 0.05$

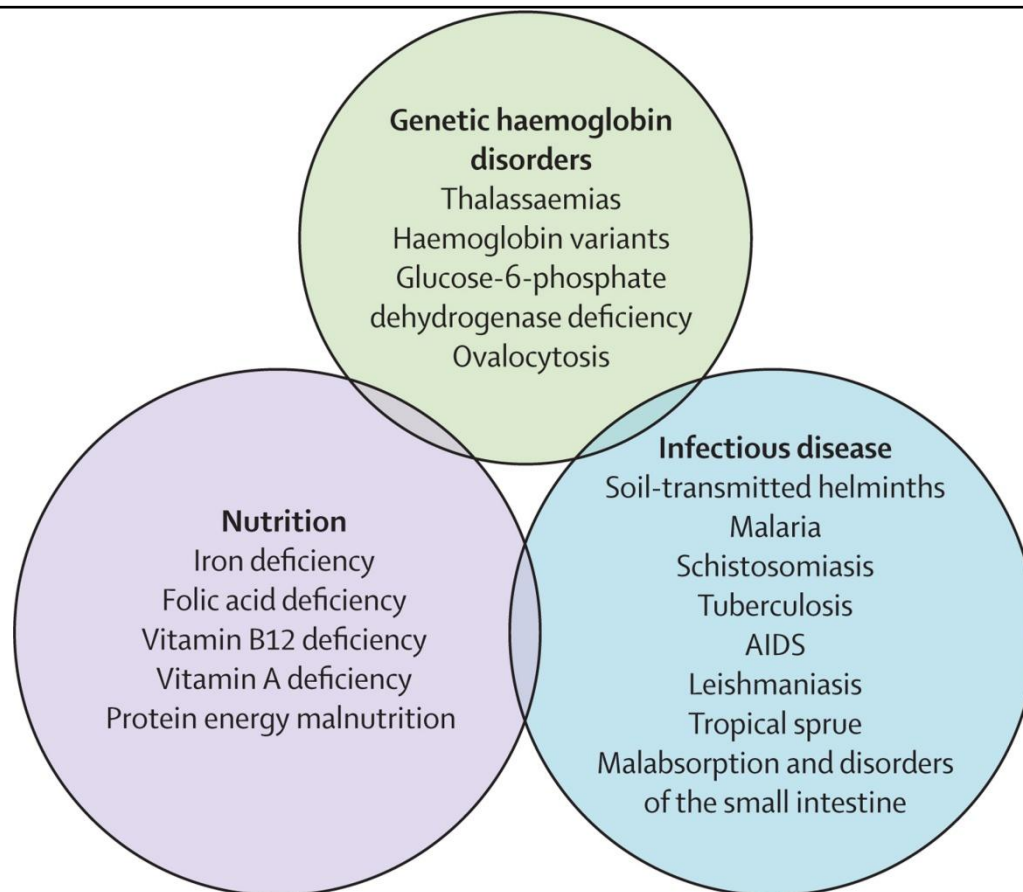


Fig. 1 Factor effect of Anaemia

Discussion

The results are helpful for deriving normative data for Hb and in delineating the degree to which iron deficiency and inflammatory disease influenced the concentration of Hb among various age/sex groups. Such data are helpful in developing rational routines for the laboratory detection of these conditions. The information also provides a base-line on which to study future trends in prevalence of Anaemia, iron deficiency, and inflammatory disease. In addition, the NHANES II data are useful as a background for public health policy decisions that pertain to the fortification of foods with iron. Anaemia is very common in elderly hospitalized patients, with a prevalence ranging from 2.9% to 66.3% (Joosten et al., 1992; Zamboni et al., 2006; Beghe et al., 2004). Possible causes for not pursuing these investigations could be death, obvious other serious pathology, such as metastatic carcinoma or severe dementia, and ignorance of the correct

work-up of Anaemia. The majority of our patients had a mild normocytic Anaemia, the most likely cause in these cases being Anaemia of chronic disease, which was confirmed with special investigations in patients. The data for adult males are of interest in showing a definite peak in Hb concentration in the early twenties with a gradual decline thereafter to median values that were 1.0 g/dl lower in the oldest age group. One distinct possibility is a decrease in an androgen stimulation of erythropoiesis that began during puberty. Another hypothesis proposed by (Lipschitz et al., 1981) is that Anaemia in otherwise healthy, aged subjects may indicate an overall reduction in hematopoietic reserve. The application of Hb reference values to elderly men will strongly influence the percentage that are considered anemic. Application of the same criteria for Anaemia to adult men of all ages might result in classifying a very large percentage of elderly men as anemic. Until there is strong

evidence to the contrary, it seems reasonable to apply age-specific reference standards to elderly men. In contrast, the lower limit of the reference range remains almost constant in women, making it practical to use the same criterion for Anaemia at all adult ages. The apparent predominance of iron-deficiency Anaemia among children, adolescents, and women during the child-bearing years is in accord with previous data (Bothwell et al., 1979; Dallman et al., 1980). Increased iron requirements for rapid growth predispose to iron deficiency in children. In women, menstrual blood loss and the iron losses associated with pregnancy are major factors. Both Anaemia and depression in the concentration of Hb related to iron deficiency and chronic disorders in NHANES II were less common than might have been anticipated from earlier surveys (Dhew 1972; JAMA 1968). However, the oversampling of poverty groups in those surveys makes it difficult to draw conclusions about trends in the United States. The populations most affected in NHANES II were children, young women, and elderly men. The pattern of laboratory abnormalities indicated that iron deficiency was the major cause of the Anaemia in infants and young women, but that inflammatory disorders played a greater role in the elderly. The prevalence of either Anaemia or a depression in Hb concentration was well below 10% in all groups. This finding is in general accord with the more limited data available from NHANES I (NCHS, 1982). It is difficult to make direct comparisons of NHANES I and II results because a number of laboratory tests, procedures, and quality control routines underwent changes between the two surveys; however, this will be the subject of a separate report from the National Center for Health Statistics. The results of NHANES II show that children and young women will continue to be the primary targets of efforts to decrease the prevalence of iron deficiency. In contrast, it cannot be anticipated that such efforts will have much influence on Anaemia in the elderly, which may prove to be more closely

related to the state of general health and to socioeconomic conditions.

Conclusion

Overall prevalence of Anaemia was high in the study population. The most common cause of Anaemia was nutritional deficiency followed by chronic kidney disease and blood loss due to antiplatelet agents. The presence of Anaemia is a risk factor for increased morbidity and in-hospital mortality in these patients. As Anaemia is a relatively frequent condition which remains often under-diagnosed and untreated, its prevention and earlier detection may lead to improved outcomes. Mothers are fostering the future citizens of our societies. The conditions for mother and child in the postpartum, nursing and lactation period should be as favorable as possible. Many young mothers have a troublesome life due to iron deficiency causing a plethora of symptoms including fatigue, physical disability, cognitive problems, and psychiatric disorders. The most reliable way to obtain this goal is to give oral ferrous iron supplements from early pregnancy in doses ranging from 30 to 50 mg daily and perform obstetric prophylactic measures in pregnancies at risk for complications.

Conflict of Interest

None of the authors of this paper have a financial or personal relationship with other people or organization that could inappropriately influence or bias the content of the paper.

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