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Very Severe Anemia Cases among Adult Patients Seen in a Nigerian Tertiary Hospital: A Review of Clinico-Laboratory Features, Differential Diagnosis and Survival

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Abstract

Background: Anemia profoundly impairs bodily health, prolongs hospital stay, heightens healthcare costs and reduces overall quality of life. Very severe ane mia (particularly acute cases) portends a critical state, may progress to irreversible vital organ damage, thereby increasing mortalities. Thus, it is worthwhile to evaluate the occurrence of very severe anemia cases, its clinical/laboratory features, prevalent causes/associations and survival patterns in Benin City, Nigeria.

Methodology: A retrospective review of 90 cases of very severe anemia who presented at the Accident and Emergency department was conducted. In this study, very severe anemia was defined as hemoglobin concentration ≤ 5 g/dl (haematocrit of 15%). Bio-data, details of clinical and laboratory findings, definitive diagnosis or associations, primary physician and survival pattern were obtained through review of case folders using a structured questionnaire. Appropriate descriptive and inferential statistics were performed.

Result: The mean ± SEM age at presentation was 44.9 ± 1.9 years. Mean haematocrit at presentation was 11.23%. About 27% of the subjects presented in anemic heart failure. Hypoproliferative anemias (55.6% of cases) were most common. The commonest causes/associations of very severe anemia were hyperhaemolytic crisis (Sickle cell disease), nutritional (substrate deficiency) anemia and upper gastro-intestinal bleeding. Anemic heart failure was significantly more associated with non-SCD (sickle cell disease) phenotype and haematocrit less than 10% (hyperanemia).

Conclusion: SCD is still associated with profound morbidities in Nigeria. Hypoproliferative anemia particularly nutritional (substrate deficiency) anemia are prevalent. Attention should be directed at holistic care of SCD in Nigeria by relevant stakeholders. Prompt triage, coupled with emergency red cell transfusion, aggressive antibiotic cover (in cases of sepsis) and other critical care is crucial to survival of affected persons.

Keywords: Sickle Cell Disease; Haematocrit; Hypoproliferative; Hyperanemia

Introduction

Anemia is a common manifestation of disease conditions among hospitalized and non hospitalized persons [1-3]. Anemia defines a clinical state in which an individual's hemoglobin concentration, haematocrit or red cell mass falls below established cut off for the persons of same age, sex and geographical location, resulting in poor tissue oxygenation [4,5]. Anemia itself is never a diagnosis but rather a manifestation of an underlying disease process. As such, proper treatment of anemia requires diagnosis and treatment of its underlying cause, not just symptomatic relief (blood transfusion) [6].

According to WHO guidelines, in a non-smoking, non-pregnant, non-African extraction individuals living at an altitude below 1000 meters, anemia is defined as hemoglobin level less than 13 g/dl in adult males above 15 years of age, 12 g/dl in non-pregnant females above 15 years and teens aged 12 to 14.99 years, 11.5 g/dl in children aged 5 to 11.99 years, 11 g/dl in children aged six months to 4.99 years [5,7]. In individuals of African origin, a cut-off of 1 g/dl lower is recommended [5,8]. Over the years, various classifications have been used in evaluating the cause of anemia. Of interest are the morphologic and the erythrokinetic approaches [6]. In terms of red cell morphology, anemias include hypochromic microcytic, normochromic normocytic and macrocytic types. Another approach is the etiologic or kinetic, which classifies anemia as haemorhagic, haemolytic or hypoproliferative types [6]. Anemia of blood loss (haemorrhage) if acute may require blood transfusion. Significant acute blood loss especially if massive or continuing requires symptomatic relief with blood transfusion and haemostatic control. Beyond surgical hemostasis and minimal invasive techniques, use of biologic and pharmacologic alternatives such as Fibrin glue helps to reduce requirements for allogeneic blood components [9]. Chronic blood loss is often associated with a relatively well-compensated anemia and iron deficiency state. Anemia of chronic blood loss is more associated with parasitic infestations in children and genital/gastrointestinal bleeding in the adult population [10].

The causes of hemolytic anemias may be intrinsic or extrinsic to the red cell. Intrinsic causes include membrane and cytoplasmic defects. Membrane defects may be inherited as in hereditary spherocytosis or acquired as in paroxysmal nocturnal hemoglobinuria. Cytoplasmic causes of hemolysis include several inherited red cell enzymopathies (commonest being glucose-6-phosphate dehydrogenase deficiency) and hemoglobinopathies [6,7]. Extrinsic sources of premature damage to the red cells includes toxaemias, infectious agents, hypersplenism, mechanical hemolytic anemias and immune mediated anemias. Approach to treatment depends on the cause of hemolysis. However, acute transfusion is usually indicated at hemoglobin concentration below 7 - 8 g/dl. Blood transfusion may be warranted at a higher transfusion threshold especially patients with existing cardiac disease [7,11]. Generally, hypoproliferative anemias include nutritional (substrate) deficiency states, aplastic anemias, anemia of chronic inflammations, marrow infiltrations, sideroblastic anemias and endocrine causes [6].

In terms of severity, WHO grades anemia into mild (10 to 10.9 g/dl), moderate (7 to 9.9 g/dl) and severe (less than 7 g/dl). Some consider very severe anemia as hemoglobin concentration less than 4 g/dl, however there is no consensus regarding this. The term, 'hyperanemia', though rarely used, refers to haemacrit value below 10% [12-14]. Severe forms of anemia are less common and may be associated with grave consequences. Acute severe anemia is more likely to present with cardiac decompensation (anemic heart failure) and/or failure of other vital organs (brain, lungs, kidneys) compared to mild grade anemia[7,15]. Due to the

critical, life threatening nature of profound (very severe) anemia, it is important to understand its clinical presentations, differential diagnosis/associations and survival pattern in index locality. This understanding will inform and direct strategies to prevent its occurrence and improve case management capacity, thus reducing morbidities and mortality.

This study therefore evaluates the clinic-laboratory features, differential diagnosis/associations and outcomes of very severe anemia cases among patients seen at the adult emergency department of a Nigerian tertiary health facility.

Methodology

This is a hospital based, retrospective cross sectional study. Patients presenting with very severe anemia at the adult emergency department of the University of Benin Teaching Hospital (UBTH), Benin City were identified in the laboratory haematocrit register. A total of 144 cases were observed to have presented with a haematocrit of 15% or less between January 2014 and June 2015. However, only 90 (62.5%) case folders could be retrieved from the hospital records department and were subjected to analysis. The other 54 case folders were missing from the library due to misplacement of these paper based records. There is no established (consensus) hemoglobin cut off for very severe anemia. However, for this purpose of this study, cases with haemocrit ≤ 15% are considered very severe anemia.

Bio-data, details of clinical and laboratory presentations, definitive diagnosis, primary physician and survival pattern were obtained through review of case folders using a structured questionnaire/proforma. At presentations in the emergency department, haematocrits were determined by micro-haematocrit (centrifugation) method [16]. Full blood count (FBC) results were retrieved in 77 subjects. FBC was determined after the initial emergency haematocrit check in the main hospital (hematology) laboratory using the automated blood cell counter (Erma Inc. Hematology Analyzer - PCE-210). In this study, leucopenia was defined as total leucocyte count less than 3000/µl and thrombocytopenia as platelet count less than 100000/ µl.

Data were inputted and analyzed using Statistical package for social sciences (SPSS Chicago USA), version 16. Descriptive statistics were performed and presented in frequencies and means. Association between occurrence of anemic heart failure and other categorical variables were tested using chi square or fisher exact test as appropriate. The level of significance was set at a probability level of 5% ($p = 0.05$).

Results

The mean age of the study population was 44.94 years (Table 1). Male to female ratio was 1:1.14. The packed red cell volume (haematocrit) at presentation in the emergency unit ranged between 5 and 15%, with a mean of 11.23% (Table 1).

Anemic heart failure (congestive heart failure, CHF) occurred in 24(26.7%) of all the subjects at presentation. Hypoproliferative anemias (55.62%) were most commonly observed (Table 2).

The most frequent (definitive) causes of very severe anemia (hyperanemia) were sickle cell disease hyperhaemolysis, nutritional (substrate deficiency) anemia and upper gastrointestinal bleeding secondary to peptic ulcer disease (Table 3). Other notable causes include myeloma/plasma cell neoplasm, myeloproliferative neoplasms, chronic lymphocytic leukaemia/lymphomas and aplastic anemia (Table 3). Seventy seven (85.6%) of all cases studied were primarily managed by hematology unit. Almost all the patients (97.8%) survived the acute events through urgent red cell transfusion. However, five of the subject died (case fatality of 5.6%) in the course of admission. The major cause of death was septic shock (overwhelming sepsis) (Table 3).

Occurrence of organ failures (anemic heart failure) was found to be more common in subjects with non-sickle cell disease hemoglobin phenotype, female gender, as well as haematocrit value of less than 10% (hyperanemia) (Table 4).

Discussion

Single cytopenia (anemia) was observed in 53% of cases. The remaining subjects had multilineage cytopenia, suggesting a defect in central (marrow) production/release of blood cells. Similarly, hypoproliferative anemias were observed to be more frequent. Hypoproliferative anemias are related to marrow failure or ineffective erythropoiesis. Generally, causes of hypoproliferative (hyporegenerative) anemia include nutritional (substrate) deficiency, anemia of chronic inflammation, sideroblastic anemia, aplastic anemia, myelophthisic anemia, endocrine anemia and renal disease [6,7]. In index study, the commonest causes of very severe anemia found included SCD hyperhaemolytic crisis, nutritional (substrate deficiency) anemia and upper gastrointestinal bleeding (Peptic ulcer disease). Multiple etiologies cannot be excluded. For instance, it is possible that a SCD patient who develops sepsis-related hyperhaemolysis could also have a background folate deficiency. However, the most pressing etiology was considered the definitive diagnosis as at the time of treatment.

Variables	Frequency(n)	Percentage (%)
Age at presentation (years)		
Less than 40	40	44.4
41 – 60	28	31.1
Greater than 60	22	24.4
Mean (SEM) = 44.94 (1.95), Median = 45, Min = 18, Max = 80		
Gender		
Male	42	46.7
Female	48	53.3
Male-Female Ratio = 1:1.14		
Presenting haematocrit*		
Less than 10%	20	22.2
10 – 15%	70	77.8
Mean (SEM) = 11.23 (0.26), Median = 11, Min = 5, Max = 15		

Table 1: Patient Characteristics (N = 90 (100%).

Variable	Frequency (n)	Percentage (%)
Clinical feature		
CHF	24	26.7
Nil CHF	66	73.3
Cytopenias		
Anemia	48	53.3
Anemia + Leucopenia	10	11.1
Anemia + Thrombocytopenia	8	8.9
Pancytopenia	11	12.2
*NA	13	14.4
Aetiologic category of anemia		
Haemorhage	9	10
Haemolysis	31	34.4
Hypoproliferative	50	55.6

Table 2: Other Clinico-Laboratory Details (N = 90(100%), *NA = Not available (77 subjects had FBC results retrieved)).

Variables	Frequency (n)	Percentage (%)
Diagnosis		
SCD hyperhaemolysis	23	25.6
Myeloma	5	5.6
Acute Leukemia	2	2.2
Chronic Kidney disease	4	4.4
Myeloproliferative neoplasm	5	5.6
Aplastic anemia	4	4.4
Septicaemia	2	2.2
Immune haemolyticanemia	3	3.3
Idiopathic thrombocytopenic purpura	1	1.1
Hyperactive malaria splenomegaly	1	1.1
Nutritional (Substrate) deficiency anemia	14	15.6
Upper GI bleeding/PUD	7	7.8
Myelophthisia (Solid tumors)	4	4.4
CLL/lymphoma	5	5.6
Paroxysmal nocturnal hemoglobinuria	1	1.1
No definitive diagnosis	9	10
Primary physician		
Haematology	77	85.6
Nephrology	3	3.3
Dermatology/HIV medicine Unit	1	1.1
Gastroenterology	8	8.9
Neurology	1	1.1
Survival of acute events		
Yes	88	97.8
No	2	2.2
Treatment outcome		
Discharged home	71	78.9
DAMA	14	15.6
Death	5	5.6
Cause of death*		
Septic shock	4	80
Hypovolaemic shock	1	20

Table 3: Differential diagnosis and survival pattern (N = 90 (100%); *5 cases of mortality, DAMA = discharge against medical advice, CLL = Chronic lymphocytic leukemia, SCD = sickle cell disease).

Variables	CHF	No CHF	X^2; *p-value*
Age groups (years)			1.702; 0.427
< 40	9	31	
41 – 60	10	18	
>60	5	17	
Hemoglobin phenotype			5.102; *0.024*
SCD	2	21	
Non- SCD	22	45	
Haematocrit groups			7.159;*0.007*;*OR = 4.00
< 10%	10	10	
10 – 15%	14	56	
Anemia category			0.148; *0.929*
Haemorhage	2	7	
Haemolysis	8	23	
Hypoproliferative	14	36	

Table 4: Association of congestive heart failure with other variables (N = 90(100%), *OR = Odd's ratio).

Severe anemia may be associated with significant organ dysfunction as a result of tissue hypoxia. If not promptly corrected, organ damage may become irreversible and death ensues. Twenty four (24) out of 90 subjects with haematocrit ≤ 15% presented in anemic heart failure. Occurrence of anemic heart failure was significantly more in subjects who were not sickle cell disease patients, females and patients with haematocrit ≤ 10 at presentation. Sickle cell disease (SCD) is associated with chronic hemolysis with resultant anemia [17]. Anemia in SCD is usually well compensated except in hyperhaemolytic crisis and other causes of worsening anemia [17,18]. Physiologic adaptations to anemia includes hyperactivity of the erythron with reticulocytosis, hyperdynamic circulation, and increased levels of 2,3-diphosphoglycerate (2,3 DPG) [15,19]. Reduced blood viscosity and higher levels of 2,3-DPG helps improve tissue oxygen delivery (with a shift of the oxygen saturation curve to the right). It is thus expected that subjects with background chronic anemia may be able to tolerate more severe forms of anemia as observed in this study.

Hyperanemia (haematocrit less than 10%) is significantly associated with heart failure at presentation. Other features of organ dysfunction such as restlessness, acute kidney injury were also observed in the cohort but were not profiled.

Most of the cases (~86%) were primarily managed by the hematology unit, followed by gastroenterology unit in 8.9% of cases. In other words, most cases (about 80%) of very severe anemia (hyperanemia) are primary hemopathies. Two of the subjects did not survive the profound acute anemia and died from irreversible organ failure. Of all the subjects, five died in the course of the admission, majorly due to overwhelming sepsis (80% of fatal cases). This suggests that severe sepsis co-existing with very severe anemia tends to reduce chances of survival in affected persons.

None of the subjects had a pre-morbid clinical history of congestive heart failure; however their baseline cardiac function prior to index presentation were not established. Based on observations from this study, congestive heart failure (CHF) in very severe anemia cases has more to do with the severity of anemia and not the cause of anemia. Haematocrit values less than 10% poses the greater risk of CHF with an odds of four. As such, the immediate clinical and laboratory presentation of anemic patients at the emergency room should guide therapeutic decisions. Patients with haematocrit less than 10% will almost always require urgent blood transfusion as an immediate measure to forestall mortality. However, some patients particularly SCD patients may not require blood transfusion at haematocrit value between 10 - 15%. Statistically, SCD patients had lower proportions of developing CHF compared to the non-SCD subjects. Although no universally accepted laboratory values exist for acute transfusion of SCD and normal subjects. Haematocrit of 10% or even higher is recommended as a transfusion trigger in SCD patients. Generally, haematocrit drop by 6% (hemoglobin concentration of 2 g/dl) or 20% haematocrit reduction from the baseline (steady state haematocrit) in an SCD patient, coupled with cardiac decompensation warrants acute transfusion [20,21]. In normal (non SCD) subjects, transfusion triggers are usually set around 21%.

Weaknesses of this study include its retrospective nature, hence an inability to distinguish between acute and chronic cases. Also, anemia was defined using haematocrit rather than hemoglobin concentrations. However, a positive linear correlation exists between haematocrit (erythrocyte centrigation method) and hemoglobin concentration [22]. Haematocrit has been shown to be reliable for routine clinical use [22]. As a rule of thumb, haematocrit is equivalent to three times the hemoglobin concentration levels. Still yet, the influence of factors such as dehydration on haematocrit values (due to plasma depletion) cannot be completely ruled out. At the point of this study, only haematocrit (microhaematocrit) check was available on emergency basis at the hospitals Accident and Emergency Unit.

Conclusion

Hyperhaemolytic crisis (Sickle cell disease) and Nutritional (substrate) deficiency are the predominant causes of very severe anemia in our setting. Concurrent severe sepsis and very severe anemia was associated with worse outcomes. Severe anemia in the setting of severe sepsis requires more aggressive treatment. All cases of very severe anemia must be investigated to determine its underlying cause and treated appropriately. Hematology review should be requested on cases of very severe anemia (particularly where haematocrit is less than 10%) except cases where clinical history/preliminary work-up suggest/confirm an obvious etiology such as massive blood loss following trauma.

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