Clinical Emergencies Presented by Anemia

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Keywords: Anaemia; Haemolysis; Haemoglobinopathies

Abstract

Anaemia affects 24.8% of the population worldwide. It has wide variety in terms of clinical manifestation of the disease severity. It can also ranges from almost asymptomatic to severe haemolytic anaemia. In contrast to all other nucleated cells, RBCs show very interesting biology. An alteration in any of the major factors in RBCs (eg, shape, size, and structural or functional or quantitional abnormalities in haemoglobin) usually results in compensatory changes in the other compensatory factors. Sometimes, the compensatory responses may fail because of severity of disease or due to underlying pathologic conditions. The result of failed compensatory responses is cellular dysfunction, tissue hypoxia and eventual cell death, which ultimately leads to severity in anaemia and emergency situations due to it.

In this paper, we have concentrated to focus on how the extrinsic and intrinsic defects on RBCs cause severe haemolytic anaemia, leading to emergencies. We have also discussed the destructions of RBCs in both extra and intra vascular regions, contributing to severe haemolysis. Other than haemolytic anaemia, other structural and functional defects of haemoglobin, which can lead to life threatening conditions (e.g.: β thalassemia major and transfusion dependent haemoglobinopathies) are also being discussed here. In nutshell, this paper is an exclusive review on all forms of clinical emergencies due to anaemia’s and other haemoglobinopathies.

Keywords: Anaemia; Haemolysis; Haemoglobinopathies

Introduction

Anaemia is defined by an absolute decrease in the number of red blood cells (RBCs), circulating in the blood. The diagnosis of anaemia is based on the laboratory measurements of RBC indices. If that found to fall below accepted normal values (Table 1) [1], then it is considered as anaemia.

<table>
<thead>
<tr>
<th>Age</th>
<th>Haemoglobin (g/dL)</th>
<th>Hematocrit (%)</th>
<th>Red Blood Cell Count (x106/μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>10.4-12.2</td>
<td>30-36</td>
<td>3.4-4.0</td>
</tr>
<tr>
<td>3-7 years</td>
<td>11.7-13.5</td>
<td>34-40</td>
<td>4.4-5.0</td>
</tr>
<tr>
<td>Adult man</td>
<td>14.0-18.0</td>
<td>40-52</td>
<td>4.4-5.9</td>
</tr>
<tr>
<td>Adult woman</td>
<td>12.0-16.0</td>
<td>35-47</td>
<td>3.8-5.2</td>
</tr>
</tbody>
</table>

Table 1: Normal values of RBC indices.

In worldwide scale, anaemia affects 24.8% of the population. It is more prevalent in children and pregnant women [2], than the adult men and women. It is also seen to be more prevalent in women than men. The prevalence of anaemia varies depending on the RBC indices used to define it. Anaemias in most cases are chronic, but it can also give rise to emergency in some special cases or clinical conditions. It can be presented as an emergency is mainly due to some clinical causes like acute blood loss or more rarely acute haemolysis or marrow involvement by hypoplasia or malignancy. More chronic types of anaemia can also be presented as an emergency, when the Haemoglobin (Hb) level falls to much lower than the normal level (Table 1), whereby the patient him or herself develops symptoms or when other disorders, e.g. myocardial insufficiency or respiratory disease co-exist.

Erythropoiesis and Anaemia

The pluripotent stem cells of bone marrow differentiate into erythroid, myeloid, megakaryocytic and lymphoid progenitors. Erythropoietin stimulates the growth and differentiation of erythroid progenitors, resulting in production of RBCs. When the normoblast extrudes its nucleus, it retains its ribosomal network, which identifies the reticulocyte. The reticulocyte keeps its ribosomal network for approximately four days, three of which are normally spent in the bone marrow and remaining one in the peripheral circulation. The RBC develops as the reticulocyte loses its ribosomal network, and the mature RBC circulates for 110 to 120 days. The old erythrocytes are destined for phagocytosis by macrophages that can detect senescence signals. Under steady-state conditions, the rate of RBC production is equal to the rate of RBC destruction, resulting the constant amount of production of RBCs. The mass of RBCs remains constant because equal numbers of reticulocytes replace the destroyed senescent erythrocytes [3].

Anaemia often can stimulate the erythropoiesis, mainly controlled by the hormone erythropoietin. Erythropoietin is a glycoprotein, produced primarily in the kidney. It regulates the differentiation of the committed erythroid stem cell and thereby controlling the production of RBCs. Tissue hypoxia and by products of RBC destruction pathway
Pathophysiology of Anaemia

RBCs are in fact the most interesting cells to follow, in biology. The physiological and biochemical processes within RBCs are markedly different from that of all other nucleated cells in our system. The major function of the RBCs is oxygen and carbon dioxide transport. RBCs transport oxygen from the lungs to the tissues and transport carbon dioxide in the reverse direction. Oxygen transport is directly influenced by the amount of haemoglobin, its oxygen affinity and flow rate of blood. An alteration in any of the major factors usually results in compensatory changes in the other factors. For example, a decrease in haemoglobin is compensated by both chronicotrophic and inotropic cardiact changes, which can result the increase in blood flow and decrease in haemoglobin affinity at the tissue level. This will ultimately allow the release of more oxygen in the tissue places. Sometimes, these compensatory responses may fail because of severity of disease or due to underlying pathologic conditions. The result of failed compensatory responses is cellular dysfunction, tissue hypoxia and eventual cell death, which ultimately leads to severity in anaemia.

Anaemias due to Haemolysis, Presenting as Emergency

A Haemolytic process must be suspected in any individual with evidence of RBC damage or change in shape, size or appearance e.g. sickle cells, spherocytes, reticulocytosis (may increase the MCV), fragmented cells (appearance in the blood film), nucleated RBCs, polychromasia and raised un-conjugated bilirubin. Family genetic history, racial origin, drug history and exposure to certain chemicals can often found useful for analyzing the root of the disease.

Common sites of unrecognized blood loss from trauma include the peritoneal, pleural, pelvic, and retroperitoneal spaces. In addition to trauma, risk factors for blood loss include acquired and hereditary abnormalities to platelets and the coagulation system. When blood loss is more than 40% of total volume, the patient may lose consciousness. With chronic anaemia, a hyper-dynamic heart, with a prominent point of maximal impulse (PMI) often present. Advanced trauma life support classifies shock into four distinct levels. Specific clinical findings are associated with each level. Class I is represented by less than 15% blood loss. Mild tachycardia may be present, but blood pressure is usually remains normal in this category of trauma. In class II, blood loss is usually 15-30%. Tachycardia, tachypnea, and decreased pulse pressure are also seen as associated symptoms in class II trauma. If, 30-40% blood gets out of the body, then it usually falls under Class III trauma. It always leads to a measurable decrease in blood pressure as well as a significant tachycardia and a narrow pulse pressure. Class IV category of trauma is categorized for more than 40% blood loss. It leads to patient demise unless prompt resuscitative measures are taken. Marked tachycardia and significantly decreased blood pressure are common findings. Blood losses greater than 50% leads to loss of pulse and blood pressure. Urinary output is decreased in class II trauma and is negligible in class IV trauma. Patients with exacerbations of chronic anaemia occasionally may present with signs and symptoms of congestive heart failure. This is especially true for the elderly persons, who are more likely to take anticoagulants and anti-platelet agents [4,5]. In non-traumatic situations of blood loss, the retroperitoneal space, gastrointestinal tract, peritoneal space, and pelvis must be considered [6].

Classification of haemolytic anaemia

There are many causes of haemolytic anaemia. Destruction of RBCs can take place at both extra-vascular (at tissue places) and intra-vascular (within the vascular network of blood flow) region. There are many different intrinsic and extrinsic causes of RBCs destruction, starting from structural and functional abnormalities of haemoglobin, the major oxygen transporter protein of RBC (eg. haemoglobinopathies including thalassaemia and sickle cell disease) to infection. The external and internal causes of Haemolytic anaemia are classified in Figure 1.

Intrinsic RBC abnormality (inherited)

Intrinsic abnormalities of RBC are the condition, in which abnormal red blood cells are the result of problems within the cells themselves. This typical Haemolytic anaemia mainly caused by mutation of genes that encodes skeletal and cell membrane haemoglobin or proteins. Defective haemoglobin or proteins cause RBC abnormalities that predispose RBC to accelerated haemolysis. These abnormalities present as intrinsic Haemolytic anaemia. There

Causes other than blood loss may be responsible for severe anaemia of rapid onset. Rare Haemolytic conditions can cause rapid destruction of RBCs. More commonly, patients with chronic compensated Haemolytic anaemia (eg. sickle cell disease, some thalassaemia etc.) have more clinically stable anaemias. Beyond red cell destruction and production, the status of haemoglobin function must be considered, because there are some inherited (eg. thalassaemia) and acquired (eg. carbon monoxide etc.) conditions, which directly influence the ability of haemoglobin to transport oxygen either by causing structural changes due to mutations (eg. thalassaemias) or by making undesired complexes with haemoglobin (eg. gas poisoning). Impaired haemoglobin transport of oxygen is seen in patients with carbon monoxide poisoning. Cyanohaemoglobinemia from cyanide, methaemoglobinemia from nitrates and sulphaemoglobinemia resulting from hydrogen sulfide can severely decrease functional haemoglobin. These patients often present with symptoms associated with anaemia, such as fatigue, shortness of breath, altered mental status and other clinical manifestations of hypoxia, but without signs of RBC loss or volume depletion [7].

Intrinsic RBC abnormality (acquired)

The primary factors that cause intrinsically abnormal RBCs fall into two categories: intrinsic defects in the RBC itself, and extrinsic factors that directly affect the RBC or its environment. Intrinsic defects in the RBC are caused by hereditary or acquired abnormalities that alter the structure or function of the RBC. Extrinsic factors that affect the RBC include infection, drugs, toxins, and other factors that may cause the RBC to become abnormal.

Intrinsic defects in the RBC include:

- Inherited disorders, such as sickle cell disease or thalassaemia, which cause the RBC to become rigid and unable to flow through small blood vessels.
- Congenital disorders, such as hereditary spherocytosis, which cause the RBC to become spherical and unable to pass through narrow blood vessels.
- Acquired disorders, such as aplastic anaemia, which cause the RBC to become abnormal due to a lack of production or destruction.

Extrinsic factors that affect the RBC include:

- Infection, such as malaria, which cause the RBC to become affected by the parasite.
- Drugs, such as chemotherapeutic agents, which cause the RBC to become affected by the drug.
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can be either membrane or metabolic defects within the RBCs or structural or functional defects associated with haemoglobin, the major structural protein of RBC.

**Membrane defect:** There are many abnormalities associated with membranes of RBCs, which can ultimately lead to severe Haemolytic anaemia. Examples include Hereditary Spherocytosis and elliptocytosis. Hereditary Spherocytosis (HS) is a familial Haemolytic disorder that affects red blood cell membrane proteins. The red blood cells are those which carry oxygen around the body. Their shape (a slightly elongated saucer) helps them to carry oxygen effectively. In Hereditary spherocytosis there is a defect in the outer layer of the red blood cell. That means the cell is not the usual shape. Spherocytosis means more sphere-shaped and this also makes it more fragile than usual. With clinically severe Hereditary spherocytosis, splenectomy is the standard treatment for patients, but can be deferred safely in patients with mild uncomplicated HS (haemoglobin level >11 g/dL). Splenectomy that usually results in full control of HS, except in the unusual autosomal recessive variant of the disorder [8]. Hereditary elliptocytosis (ovalocytosis) is a rare autosomal dominant disorder in which RBCs are elliptical or oval or are poikilocytic and bizarrely shaped [9]. These disorders are clinically, genetically, and biochemically heterogeneous [10]. Hereditary elliptocytosis, that is due to defects in either the structure or quantity of the cytoskeletal proteins which is responsible for maintaining the biconcave morphology of RBCs. Mutations in either alpha- and beta-spectrin are most commonly responsible, but mutations in other cytoskeletal proteins (band 4.1 and glycophorin) are also described [11].

**Metabolic defect:** Metabolic defects within RBCs can also contribute to Haemolytic anaemia. Glucose-6-phosphate dehydrogenase deficiency (Shunt pathway) and pyruvate kinase deficiency (Embden-Meyerhof pathway) can lead to Haemolytic anaemia (Figure 2).

**Extrinsic RBC abnormality (acquired)**: Extrinsic abnormalities of RBC are the abnormalities of the red blood cells that are mostly due to a disorder, disease or condition outside of the red blood cells themselves.

Extrinsic Haemolytic anaemia is often due to immune mechanisms, as in warm and cold agglutinin Haemolytic anaemia. However, there are many non-immune causes, which includes systemic diseases, mechanical destruction (i.e., fragmentation haemolysis), and also increased the destruction within an enlarged spleen (hypersplenism), and the action of toxins and drugs.

**Autoimmune haemolytic anaemia:** Autoimmune haemolytic anaemia is a group of disorders which is characterized by a malfunction of the immune system that produces autoantibodies, which attack the red blood cells as if they were substances foreign to the body. The lifetime of the RBCs is reduced from the normal 100–120 days to just a few days in serious cases [13,14]. Haemolytic disease of the newborn (HDN) – also called erythroblastosis fetalis. It is a blood disorder that occurs when the blood types of a mother and baby are incompatible [4] HDN used to be a major cause of fetal loss and death among newborn babies. It occurs when baby's red blood cells break down at a fast rate.

The most common form of Haemolytic disease of the newborn is ABO incompatibility, that is usually not very severe. Other, less common types may cause the more severe problems. The least common form of HDN is Rh incompatibility, which can almost always be prevented. If this form does occur, it can cause very severe anaemia in the baby.

**Lever disease:** Red cell fragments are especially formed when the fibrin strands come in contact with the circulating red cells. The
strands are cut a small piece from the original cell. Several descriptive names have been used for fragmented red cells, depending on the resulting shape of the fragment. Those include pre-keratocyte (blist cell), schistocyte (more of a catch-all term), and keratocyte (horn cell or helmet cell).

**Intra-vascular haemolysis**

There are many causes of Haemolytic anaemia. When destruction of RBCs take place at intra-vascular (within the vascular network of blood flow) network, that are considered as Intra-vascular Haemolysis.

**Transfusion reactions:** Transfusion reactions are very important, that the blood is accurately matched to the donor and recipient type. If the blood type does not match, it can produce severe transfusion reaction. These reactions are mostly rare, but they can affect the kidneys and lungs (Figure 3).

**Antibody-mediated Acute haemolytic reactions:**

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Compatible Red Cell Types</th>
<th>Compatible Plasma Types (YP A Cryo-precipitate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RhD-positive</td>
<td>RhD positive</td>
<td>RhD negative</td>
</tr>
<tr>
<td>RhD-negative</td>
<td>RhD negative</td>
<td>RhD positive</td>
</tr>
<tr>
<td>A</td>
<td>A, O</td>
<td>A, AB</td>
</tr>
<tr>
<td>B</td>
<td>B, O</td>
<td>B, AB</td>
</tr>
<tr>
<td>O</td>
<td>O</td>
<td>A, B, AB</td>
</tr>
<tr>
<td>AB</td>
<td>A, AB, B, O</td>
<td>AB</td>
</tr>
</tbody>
</table>

**Figure 3:** List of antibody mediated acute Haemolytic reactions.

**Blood and plasma compatibility.**

**Micro-organopathic trauma:** Micro-organopathic trauma includes thrombotic thrombocytopenic purpura, Haemolytic uremic syndrome, Pre-eclamptic toxemia (PET), meningococcal septicaemia etc. Thrombotic thrombocytopenic purpura (TTP) that is a blood disorder that causes blood clots to form in small blood vessels. This leads to a low platelet count (thrombocytopenia). Haemolytic uremic syndrome (HUS) is a condition that results from the abnormal premature destruction of the red blood cells. If this process begins, then the damaged red blood cells start to clog the filtering system in the kidneys, which may eventually cause the life-threatening kidney failure associated with Haemolytic uremic syndrome. Pre-eclamptic toxemia (PET) is also called Toxemia of Pregnancy or Pregnancy induced hypertension. This syndrome develops after the 20th week of pregnancy. Disseminated intravascular coagulation is one type of serious disorder in which the proteins that control blood clotting become overactive. This can reduce blood flow and also can block blood from reaching bodily organs. As the condition progresses, the platelets and clotting factors in blood are used up, and it will begin to experience excessive bleeding. Meningococcal septicaemia is the blood poisoning form of the disease and also it is the more life threatening form of the disease and more dangerous when there are no signs of meningitis.
Infections: Infection can also cause the RBC haemolysis. The common infections include *Plasmodium falciparum*, *Clostridium welchii*, *Mycoplasma pneumonia* etc. *Plasmodium falciparum* is the protozoan parasite, and one of the species of *Plasmodium* that can cause malaria in humans. It is transmitted by the female *Anopheles* mosquito. Malaria caused by this species (also called malignant or *falciparum* malaria) is mostly dangerous form of malaria, with the highest rates of complications and mortality. *Clostridium welchii* type A is the most common agent of food poisoning when allowed to proliferate to the large numbers in cooked foods, usually meat and poultry. The main factors are survival of the spores, frequently found on the raw products, through the cooking process and possible contamination of cooked meats transferred to the unclean containers; subsequent germination of spores and also the rapid multiplication of the vegetative cells during long slow cooling and non-refrigerated storage lead to the heavy contamination. The toxin responsible is different from the soluble antigens, and its formation in the intestine which is associated with sporulation. *Mycoplasma pneumonia* is an infection of the lungs by the bacteria *Mycoplasma pneumonia* and also a common cause of community-acquired pneumonia and the disease usually has a prolonged, gradual onset [15]. The disease spreads very easily through contact with respiratory fluids, and it causes regular epidemics. Infectious mononucleosis is an infection usually caused by the Epstein-Barr virus. This virus spreads through saliva that is why it sometimes called "kissing disease." Mono occurs most often in teens and young adults. Infectious mononucleosis was first described by Sprunt and Evans in the Bulletin of the Johns Hopkins Hospital in 1920 [15].

Paroxysmal nocturnal haemoglobinuria: Paroxysmal nocturnal haemoglobinuria is a rare disease in which red blood cells break down earlier than normal. This disease is characterized by the destruction of red blood cells (Haemolytic anaemia, impaired bone marrow function), blood clots (thrombosis) and a 3 to 5% risk of the developing leukaemia. Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired clonal disorder in which the intravascular haemolysis results from the somatic mutation of the totipotent stem cells, causing an intrinsic defect in the red cell membrane [16].

March haemoglobinuria: March haemoglobinuria haemolysis caused by repeated uncushioned shocks or trauma to some boy part, such as in some soldiers on long marching, in marathon running, and in karate practitioners.

Prospective Management and Discussion

Patients with a compensated Haemolytic process require no treatment. Folic acid 5 mg daily is given life-long in those with symptomatic Haemolytic disorders. Therapeutic approaches to treat anaemia include blood and blood products, hormonal/nutritional therapies, immune-therapies and adjunctive therapies. The aim of the therapy in acute anaemia is to restore the haemodynamics of the vascular system and to replace lost red blood cells (RBCs). Mineral and vitamin supplements, vasopressors, blood transfusions, glucocorticosteroids and histamine (H2) antagonists are generally used to achieve this. Correction of acute anaemia often requires blood, blood products, or both. Transfusion of blood alone is insufficient if there is significant on-going haemolysis or haemorrhage. But providing transfusion timely to restore haemoglobin to safe levels can prevent major complications of acute anaemia. Although RBC transfusion is the quickest way to raise the haemoglobin concentration, that benefit must be balanced against the significant complications associated with transfusion. Multiple studies have reported worse outcomes (e.g. higher morbidity and mortality rates) in transfused patients compared with non-transfused or less-transfused patients. Whole blood contains RBCs, platelets, and coagulation factors. But the whole blood is rarely used as a treatment option, as every patient does not need all the components of the blood. So, a given blood of a single donor can be separated in components and can serves the purpose of more the one patients. Packed red blood cells (PRBCs) are the remaining components of whole blood after the platelets and plasma are removed. Each unit of PRBCs is expected to raise the haematomcitocrit (Hct) level by 3. There are associated complications with the use of blood and blood products. Blood products have the potential to transmit bacterial and viral diseases too. Bacterial or viral contamination is the most common infectious risk of blood transfusion. Immunological responses are also associated with blood transfusion. So, washed packed cells used for patients with lesser immunological tolerance level. Other complications of transfusion therapy include volume overload, allergic reactions, anaphylaxis, hypothermia, hypocalcaemia and disseminated intravascular coagulation (DIC).

If transfusion cannot be given due to other associated clinical situations, erythropoietin and iron supplements in the sub-acute phase may be beneficial. Currently, research is on-going to evaluate the effectiveness of inorganic compounds, such as dodecafluoropentane emulsion (DDFPe) as a blood substitute. It (DDFPe) is an inorganic fluorocarbon compound, which expands at body temperature and has a strong affinity for oxygen [17]. Poly-Heme is an oxygen-carrying blood substitute made from human blood [18], which can be an excellent option for those willing to receive human-blood-derived products. The advantages of Poly-Heme are that, it has shelf life of more than 1 year, does not require cross-matching and has virtually no risk of transmitting infections. Other blood substitutes are also under research, including hyper viscous plasma expanders such as polyethylene glycol conjugate albumin [19].

References


