Relation between D-dimer test, arterial blood gases analysis and pulmonary hypertension in patients with chronic hemolytic anemia

Thesis

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Introduction

Hemolytic anemia is defined as anemia due to a shortened survival of circulating red blood cells (RBCs).Although the time of RBC senescent death in adults is 110 to 120 days, it is convenient to define hemolysis as a shortening of RBCs survival to a value of less than 100days ***(Franco, 2009).***

Echocardiographic estimation of pulmonary artery pressure by measuring the tricuspid valve regurgitant jet velocity (TRV) has been validated as a useful screening method for pulmonary hypertension in adult patients with sickle cell disease ***(Gladwin et al., 2004).*** A jet velocity of 2.5 m/sec or more, which corresponds to a systolic pulmonary artery pressure of 30 mmHg or more, has been used for research purposes to define elevated pulmonary artery pressure in adults with sickle cell disease ***(Ataga et al., 2004; Castro & Gladwin., 2005).***

Pulmonary hypertension is an increasingly recognized complication of chronic hereditary and acquired hemolytic anemias, including sickle cell disease (SCD), thalassemia intermedia and major, paroxysmal nocturnal hemoglobinuria,hereditary spherocytosis and stomato-cytosis, microangiopathic hemolytic anemias, pyruvate kinase deficiency and possibly malaria ***(Machado et al.,2005 and Rother et al.,2005).***

The inherited hemoglobin disorders sickle cell disease and thalassemia are the most common monogenetic

disorders worldwide. Hemolytic disorders are potentially among the most common causes of pulmonary hypertension. Pulmonary hypertension is one of the leading causes of morbidity and mortality in adult patients with sickle cell disease and thalassemia ***(Roberto et al., 2010).***

The pathogenesis of pulmonary hypertension in hemolytic disorders is likely multifactorial, including hemolysis, impaired nitric oxide (NO) bioavailability, chronic hypoxemia, chronic thromboembolic disease, chronic liver disease and asplenia ***(Roberto et al., 2010).***

Epidemiologic risk factors suggested to be associated with PHT in patients with hemolytic anemia include the following: markers of hemolysis in the form of low hemoglobin levels, high reticulocytic count and high serum bilirubin ***(Ersi et al., 2007 and Caterina et al., 2009)***, increased systolic blood pressure ***(Paul et al., 2007 and Caterina et al., 2009)***, hypercoagulability including D-Dimer level ***(Atagaet al., 2008)*** and lower oxygen satuaration ***(Uong et al.,2006).***

There is increasing evidence that sickle cell disease (SCD), as well as other chronic hemolytic anemias such as β thalassemia, paroxysmal nocturnal hemoglinuria, autoimmune hemolytic anemia and unstable hemo-globinopathies, are characterized by a hypercoagulable state***(Ataga et al., 2007).***

Coagulation disorders, such as low levels of protein C, low levels of protein S, high levels of D-dimers and

increased activity of the tissue factor, occur in patients with sickle cell anemia***(Berneyet al., 1992).***

Markers of coagulation activation appeared to be higher in SCD patients with pulmonary hypertension than in those without ***(Ataga, et al.,2008).***

Arterial blood gasesanalysis and Oxygen saturation (SaO2) below normal measurements for patients with SCD are useful in early detection and monitoring for the presence of pulmonary complications as pulmonary hypertension ***(Rackoff et al.,1993).***

Oxygen saturation (SaO2) measurements by pulse oximetry are below normal in patients with SCD ***(Uong et al.,2006).***

Hypoxia contributes to sickle cell-related pulmonary hypertension as Humans exposed to chronic hypoxia have a tendency to develop pulmonary hypertension. Patients with sickle cell disease may experience chronic hypoxia due to anemia, upper airway obstruction, chronic hemoglobin oxygen desaturation and repeated episodes of vaso-occlusive pain crisis or acute chest syndrome. Hypoxia might, therefore, be a factor in the development of pulmonary hypertension in patients with sickle cell disease ***(Minniti et al., 2009).***

The pulmonary arterial circulation has low oxygen tension and low pressure facilitate the polymerization of sickle hemoglobin,causing both acute and chronic pulmonary manifestations as pulmonary hypertension***(Powars et al.,1988).***

Hemolytic Anemia

Hemolytic anemia is defined as anemia due to a shortened survival of circulating red blood cells (RBCs).Although the time of RBC senescent death in adults is 110 to 120 days, it is convenient to define hemolysis as a shortening of RBCs survival to a value of less than 100 days ***(Franco,2009).***

The abnormal breakdown of red blood cells is either in the blood vessels(intravascular hemolysis) or elsewhere in the body (extravascular). It has numerous possible causes, ranging from relatively harmless to life threatening.Hemolytic anemias can be classified to immune and non immune,acute or chronic and hereditary or acquired. Management depends on the cause and nature of the breakdown. Hemolytic anemia represents approximately 5% of all anemia's***(Paul Schick, 2009).***

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Table (1): Overview of the Hemolytic Anemias:

Type	Etiology	Associations	Diagnosis	Treatment
Acquired				
Immune-mediated	Antibodies to red blood cell surface antigens	Idiopathic malignancy drugs autoimmune disorders infections transfusions	Spherocytes and positive DAT	Treatment of underlying disorder; removal of offending drug; steroids, splenectomy, IV gamma globulin, plasmapheresis, cytotoxic agents, or danazol (Danocrine); avoidance of cold
Microangiopathic	Mechanical disruption of red blood cell in circulation	TTP, HUS, DIC, pre-eclampsia, eclampsia, malignant hypertension, prosthetic valves	Schistocytes	Treatment of underlying disorder
Infection	Malaria, babesiosis, Clostridium infections		Cultures, thick and thin blood smears, serologies	Antibiotics
Hereditary				
Enzymopathies	G6PD deficiency	Infections, drugs, ingestion of fava beans	Low G6PD activity measurement	Withdrawal of offending drug, treatment of infection
Membranopathies	Hereditary spherocytosis		Spherocytes, family history, negative DAT	Splenectomy in some moderate and most severe cases
Hemoglobinopathies	Thalassemia and sickle cell disease		Hemoglobin electrophoresis, genetic studies	Folate, transfusions

DAT = direct antiglobulin test; IV = intravenous; TTP = thrombotic thrombocytopenic purpura; HUS = hemolytic uremic syndrome; DIC = disseminated intravascular coagulation; G6PD = glucose-6-phosphate dehydrogenase.

(Gurpreet et al., 2004)

BETA-THALASSEMIA

Beta-thalassemia syndromes are a group of hereditary blood disorders characterized by reduced or absent beta globin chain synthesis, resulting in reduced Hb in red blood cells (RBC), decreased RBC production and anemia ***(Galanello and Origa, 2010).***

Thalassemia was described as a clinical entity for the first time in 1925 by Dr. Thomas B. Cooley and his associate Pearl Lee as a form of severeanemia, occurring in children of Italian origin and associatedwith splenomegaly and peculiar bone changes ***(Olivieri, 1999).***

The word "thalassemia" comes from the Greek word "thalassa" (sea) because of the high prevalence of the disease in the countries bordering the Mediterranean Sea. However, immigration of those populations to USA, Canada, and Western European countries has resulted in a more universal distribution of the disease ***(Kremastinos et al., 2007; Modell et al., 2000 and Olivieri et al., 1994).*** Therefore, beta-thalassemia should currently be considered a global rather than a regional health problem.

Incidence:

Thalassemia syndromes are the most common single-gene disorder worldwide. About 3% of the world population carries the β-thalassemia genes ***(DeBaun et al., 2011).***The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the

world and 1 in 10,000 people in the European Union ***(Vichinsky, 2005).***In Egypt, beta-thalassemia is the most common type of hemolytic anemia. Carrier rate varying from 5.3 to > or =9%. It was estimated that 1,000/1.5 million per year live births will suffer from thalassemia disease in Egypt ***(El-Beshlawy and Youssry, 2009).***

Table (2): Beta-thalassemias Classification:

1. Beta-thalassemia ▪ Thalassemia major ▪ Thalassemia intermedia ▪ Thalassemia minor
2. Beta-thalassemia with associated Hb anomalies ▪ HbC/Beta-thalassemia ▪ HbE/Beta-thalassemia ▪ HbS/Beta-thalassemia (clinical condition more similar to sickle cell disease than to thalassemia major or intermedia)
3. Hereditary persistence of fetal Hb and beta-thalassemia
4. Autosomal dominant forms
5. Beta-thalassemia associated with other manifestations ▪ Beta-thalassemia-tricothiodystrophy ▪ X-linked thrombocytopenia with Thalassemia

(Galanello and Origa, 2010)

Diagnosis of Beta Thalassemia:

1) Clinical Diagnosis:

Thalassemia was defined as a clinical entity for the first time in five young children presenting with severe anemia, splenomegaly, bone abnormalities ***(Weatherall,2004).***Although the clinical phenotypes of thalassemia minor, intermedia and major differ, there are some similarities. There is an increasing awareness of the need for accurate diagnosis in order to achieve optimal patient management and to avoid over or under treatment (***Camaschella& Cappellini, 1995 and Galanelloand Cao, 1998).***

- **Anemia:**

Hypochromic microcytic anemia becomes apparent 3-6 mo after birth when the switch from γ to β chain production takes place ***(Quirolo et al., 2004).***Manifestations of anemia include extreme pallor and enlarged abdomen due to hepatosplenomegaly. Severe anemia is manifested by intolerance to exercise, heart murmur, or even signs of heart failure ***(Yaish, 2007).***

- **Skeletal changes:**

It occure due to massive erythroid marrow hypertrophy in medullary and extramedullary sites. In the long bones, marrow expansion results in cortical thinning and pathologic fractures and the marrow spaces of the cranial vault markedly expand**.** These changes may result in

cosmetic abnormalities that can cause emotional distress. Expanding paravertebral EMH may compress the spinal cord ***(Pearson, 1997).***These changes in thalassemia occure as a result of long term hypoxia and the consequences of therapy ***(Lawson et al., 1981).***

- **Splenomegaly:**

The constant exposure of the spleen to red cells with inclusions of precipitated globin chains causes splenomegaly in both α and β thalassemia and may exacerbate the anemia ***(Weatherall, 1994).*** With the gross splenomegaly that may occur, secondary thrombocytopenia and leucopenia frequently develop leading to a further tendency of infection and bleeding ***(Weatherall, 2001).*** The spleen progressively enlarges; it often requires a splenectomy to relieve the mechanical burden ***(Pearson, 1997).***

- **Other features:**

Jaundice is almost always present with variable severity. Growth retardation also is a common finding. Patients may develop symptoms that suggest diabetes, thyroid disorder, or other endocrinopathy ***(Yaish, 2007)***. Many of the thalassemic patients have viral hepatitis which may augment liver damage ***(El-Beshlawy et al., 1989).***

Clinical Squeal in Beta Thalassemia:

Various complications are common in Patients with TI more than TM patients including: pulmonary hypertension (PHT), thrombosis, folic acid deficiency, gallstones, leg ulcers, infertility, and extramedullary hematopoiesis ***(Camaschella et al., 1995).***

Pulmonary hypertension and congestive heart failure:

Cardiac involvement represents the leading cause of mortalityin both forms of ß-thalassemia, namely, TM and TI, and PHT is part of the cardiopulmonary complications of the disease ***(Aessopos and Farmakis, 2005).***

Two main factors determinecardiac disease in this form. One is the high output state that results from chronic tissue hypoxia and from hypoxia-inducedcompensatory reactions. The other is the vascular involvementthat leads to an increased pulmonary vascular resistance andan increased systemic vascular stiffness ***(Aessopos et al., 2007A).***

Thromboembolic events:

Patients with TI have an increased risk of thrombosis compared with a normal age and sex-matched population and with TM patients ***(Taher et al., 2006B).***

In TI patients, these events primarily occurred in the venous system and comprised deep vein thrombosis (DVT) (40%), portal vein thrombosis (19%), stroke (9%),

pulmonary embolism (12%) and others (20%). Moreover, splenectomized non-transfused patients with a low hemoglobin level (<9g/dl) have a higher risk of thrombosis ***(Taher et al., 2006B).***

Folic acid deficiency:

Folic acid deficiency is common in TI and occurs due to poor absorption, low dietary intake, or, most significantly, an increased demand for folic acid from active bone marrow ***(Taher et al., 2009).***

Cholelithiasis:

Gallstones are much more common in TI than in TM because of ineffective erythropoiesis and peripheral hemolysis. Recently, unrelated genetic factors such as uridine 5' diphospho-alpha-D-glucose (UDPG) deficiency (Gilbert's syndrome) have been reported to increase gallstone formation in patients with thalassemia ***(Borgna-Pignatti et al., 2003).***

For this reason, the gallbladder should be inspected during splenectomy and a cholecystectomy performed if necessary, particularly if the patient is experiencing symptomatic gallstones. This should be undertaken to prevent cholecystitis, which can have serious consequences in the splenectomized patient ***(Taher et al., 2009).***

Leg ulcer:

Leg ulcers are common in TI. Several factors contribute to their pathogenesis: chronic anemia, reduced oxygen delivery to the distal regions, venous stasis and erythrocytes rheologic abnormalities ***(Camaschella and Cappellini, 1995).***

Pregnancy and Infertility:

Patients with TI have normal puberty and may have normal sexual development ***(Scordis et al., 1998).*** Although fertility is compromised in patients with transfusion-dependent TM, pregnancy is possible in the majority of patients with TI ***(Taher, 2007).***

The chronic anemia of TI can cause an increase in spontaneous abortions, preterm labour and intrauterine growth retardation, while endocrine complications due to hemo-siderosis are common ***(Skordis et al., 1998).***

Extramedullary hematopoiesis:

Extramedullary hematopoiesis (EMH) is a compensatory mechanism where bone marrow activity increases in an attempt to overcome the chronic anemia of TI, leading to the formation of erythropoietic tissue masses that primarily affect the spleen, liver and lymph nodes. These masses can be detected by magnetic resonance imaging (MRI). They may cause neurological problems such as spinal cord compression and paraplegia, and intrathoracic masses ***(Chehal et al., 2003; Castelli et al., 2004).***

2) Laboratory Diagnosis:

a. Hematological diagnosis:

The complete blood count (CBC) and peripheral blood film examination results are usually sufficient to suspect the diagnosis ***(Yaish, 2005).***The patient's Hb level can be maintained at 6-7 g/dl without blood transfusions ***(Yaish, 2007).***

Affected individuals show RBC morphologic changes [microcytosis, hypochromia, anisocytosis, poikilocytosis (spiculated tear-drop and elongated cells)] ***(Collins et al., 2002).*** A reticulocytic count though elevated (5-15%) is lower than would be expected from the degree of marrow erythroid hyperplasia and hemolysis probably due to intramedullary destruction ***(Alter, 2002).***

The white cell and platelet counts are slightly elevated unless there is secondary hypersplenism ***(Weatherall, 2001).***

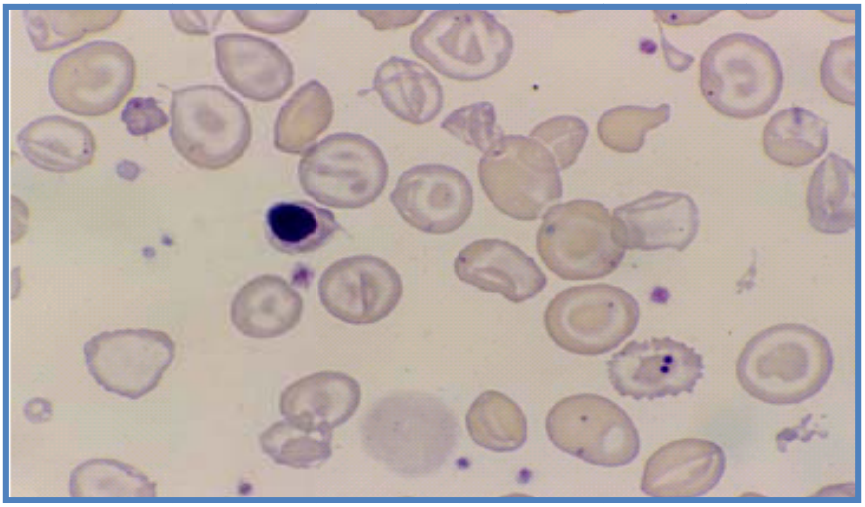

Fig. (1): β-thalassemia. Note the bizarre erythrocyte morphology and the nucleated erythrocyte ***(Kerm, 2002).***

b. Biochemical studies:

- *Measurement of iron stores:*

The severity of iron loading in patients with β-thalassemia is assessed from transfusion history, as well as through determination of serum iron, total iron binding capacity and serum ferritin concentration ***(Olivieri, 1994)***,and assessment of liver iron concentration (LIC) from biopsy tissue ***(Pakbaz et al., 2007).***

Many patients with TI have serum ferritin and LIC levels above the recommended threshold levels identified in patients with TM. Serum ferritin levels were seen to increase with age, reflecting increased iron accumulation over time, even in the absence of transfusion therapy ***(Pakbaz et al.,2007).*** Hepatic iron concentration and liver histology should be assessed at intervals every 1–2 years in patients receiving chelating therapy ***(Olivieri, 1997).***