

# Review Article

## Acquired Hemoglobin Disorders

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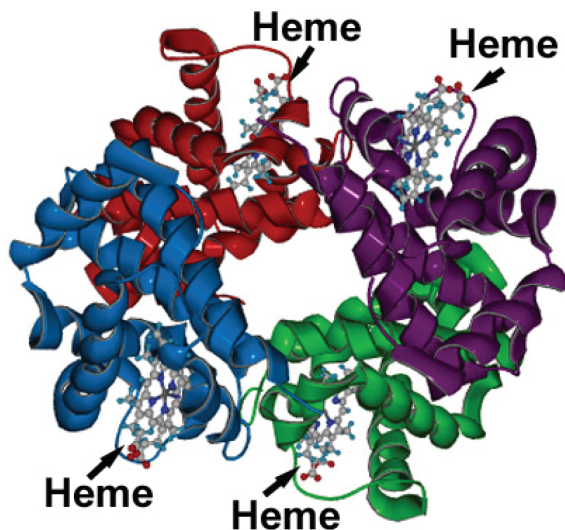
### Abstract

Hemoglobin is made of Heme and globin and disorders of hemoglobin can be due to abnormality in either one of them. More than 1000 genetic mutations have been identified to cause hemoglobin disorders. Mutations can affect heme molecule and cause disorders like Methemoglobinemia. Mutations affecting globin chains are called Hemoglobinopathies and can be quantitative (thalassemia) or qualitative (sickle cell Anemia). Hemoglobin disorders are mostly inherited and only a few are acquired. In this article we discuss about the structure of heme and globin molecules, abnormalities that can occur in them and review about Acquired Heme and Globin disorders. Acquired heme disorders are Methemoglobinemia and Sulfhemoglobinemia and an example for acquired globin disorder is alpha thalassemia.

**Key Words:** Acquired hemoglobin disorder, Methemoglobinemia,  $\alpha$  Thalassemia, Sulfhemoglobinemia, Myelodysplastic syndrome

### Introduction

Hemoglobin is a spherical molecule present within RBC and is made of 4 heme and 4 globin chains and it carries oxygen.



**Fig 1 :** Structure of Hemoglobin  
(Figure Courtesy Wikipedia)

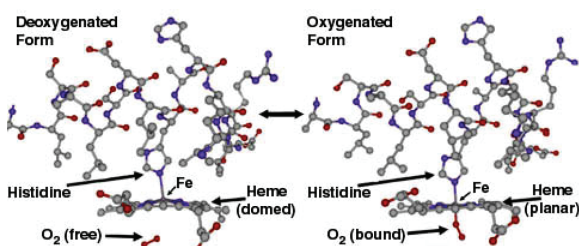
Each heme has 1 iron in the center of protoporphyrin. This iron attaches to Oxygen ( $O_2$ ) on one side and to globin chain on the other side through the histidine amino acid of the globin chain. Each iron binds to 1 molecule of oxygen, so 1 hemoglobin molecule can carry 4 molecules of Oxygen. This binding of iron with oxygen is reversible.

### Abnormalities that can occur in Heme Molecule

Heme exists in 2 states, Oxy state also called R state (Relaxed State) when iron binds with Oxygen and Deoxy state also called T state (Tense State) when iron gives up oxygen<sup>1</sup>. Iron in heme exists normally as ferrous form. When oxygen attaches to the ferrous iron of 1 heme group, conformational change occurs in the surrounding globin chains. This change in shape makes it easier for the other three heme groups to become oxygenated. This enhancement in the ability of hemoglobin molecule to bind more oxygen is called "cooperative binding"<sup>1</sup>. But if ferrous form is converted to ferric form it results in methemoglobinemia where oxygen affinity is altered leading to poor oxygen delivery to tissues. Similarly when sulfur binds to heme and produces sulfated heme, oxygen affinity is altered.

### Abnormalities that can occur in Globin chains

Normal hemoglobin has 4 globin chains in the form of a tetramer. There are 4 different globin chains alpha, beta, gamma and delta. A tetramer is formed by combination of 2 of these chains, in dimers. Normal adult hemoglobin (HbA) has 2 alpha and 2 beta chains ( $\alpha_2\beta_2$ ), while fetal hemoglobin (HbF) has 2 alpha and 2 gamma chains ( $\alpha_2\gamma_2$ ) and second adult type (HbA<sub>2</sub>) has 2 alpha and 2 delta chains ( $\alpha_2\delta_2$ ). A tetramer formed of such a dimer combination makes it more stable. But when a tetramer is formed of 4 monomers



**Fig 2 :** Binding of iron with  $O_2$  and globin chains

of same chain called homotetramer as in Thalassemias, the tetramer becomes unstable and forms inclusions within RBCs.

Also, synthesis of globin chains is controlled by multi-gene clusters. Multigene clusters in chromosome 16 control alpha chain synthesis and multigene clusters in chromosome 11 control beta chain synthesis. In addition, there are also regulator genes which control the expression of these globin genes. Mutations in these multigene clusters or in the regulator genes cause thalassemia. Thalassemia occurs because of quantitative defects in globin chains. Thalassemias can be alpha or beta thalassemia. Mutations causing beta thalassemia are mostly point mutation while mutations causing alpha thalassemia are mostly deletion mutations<sup>2</sup>.

## Acquired Heme disorders

Under this we discuss Methemoglobinemia and Sulfhemoglobinemia

### Methemoglobinemia

It is a disorder in heme molecule. In this disorder, ferrous form ( $\text{Fe}^{2+}$ ) of iron is oxidised to ferric form ( $\text{Fe}^{3+}$ ) and Hemoglobin becomes Methemoglobin. When iron in one of the four heme molecules is converted to ferric form, certain conformational changes occur in the heme group increasing the affinity of the remaining heme for Oxygen. So they bind more  $\text{O}_2$  and also do not give  $\text{O}_2$  to tissues causing tissue hypoxia. Methemoglobin thus formed gives a slate grey colour to the blood and resembles cyanosis (Pseudo cyanosis).

Normal Methemoglobin level is 0 - 2%. When methemoglobin level is > 10%, there is cyanosis and when levels go > 30% it leads onto cerebral and cardiovascular hypoxic symptoms. These hypoxic symptoms and cyanosis also do not respond to supplemental oxygen. Though these patients are cyanotic, Oxygen saturation ( $\text{SaO}_2$ ) and Partial pressure of Oxygen ( $\text{PaO}_2$ ) are normal, this is the most important clue for differentiating from other causes of cyanosis. Methemoglobin is best diagnosed by spectrophotometer and gas chromatography. Methylene blue by reducing ferric iron to ferrous iron is the treatment of choice.

But not all patients with Methemoglobinemia respond to treatment with Methylene blue. Methemoglobinemia can be congenital or acquired. Congenital Methemoglobinemia is a rare autosomal recessive disorder occurring due to mutation in gene controlling the production of Nicotinamide Adenine Dinucleotide Hydrogen (NADH) Cytochrome b<sub>5</sub> reductase enzyme (the enzyme which helps in reducing Ferric iron to ferrous iron) causing a deficiency in this enzyme<sup>3</sup>. This congenital form does not respond to treatment with Methylene blue.

On the other hand, Acquired Methemoglobinemia is a more common disorder. This occurs on exposure to oxidising agents present in drugs or toxins. Common drugs causing it are Sulphonamides, Sulphasalazine, Dapsone, Chloroquine, Primaquine, Nitroglycerine,

Phenytoin and Sodium valproate. These drugs oxidize the ferrous form to ferric form producing Methemoglobin. Such hemoglobin also becomes denatured and form inclusions within RBC called Heinz bodies. This leads to hemolysis. Methemoglobinemia also can occur in sepsis where Nitric Oxide (Oxidising agent) levels are high. Acquired methemoglobinemia responds to treatment with Methylene blue. Methylene blue absorbs the  $\text{O}_2$  attached to Ferric form and the Nicotinamide Adenine Dinucleotide Dehydrogenase (NADH) present within RBC reduces Ferric to ferrous form of iron. So NADH is required for the conversion. Dextrose infusion is also given for increasing NADH production within RBC through Glycolytic pathway<sup>3</sup>.

### Sulfhemoglobinemia

This is also a heme disorder. Here sulfur atom is incorporated into protoporphyrin ring forming sulfated heme. Once formed, sulfated hemoglobin persists throughout the RBC life span and this conversion is irreversible. This creates a conformation change in the other heme molecules decreasing their oxygen affinity. This is unlike methemoglobinemia where there is marked increase in  $\text{O}_2$  affinity.

Sulfhemoglobinemia is less common, milder and less symptomatic disease than methemoglobinemia but the cyanosis colour is bluer<sup>4</sup>. This occurs commonly with exposure to sulpha drugs and environmental pollution. In some it occurs in combination with methemoglobinemia and is called sulfmethemoglobinemia. This occurs because many oxidising agents causing methemoglobinemia have sulfur atoms and sulfur also get incorporated. This combination is less toxic than pure methemoglobinemia as the  $\text{O}_2$  affinity is less and so oxygen delivery to tissues is facilitated. Normally, the bluish discoloration with sulfhemoglobinemia occurs when sulfhemoglobinemia level is > 0.5 gm%. Level required by Methemoglobin to produce similar cyanosis is > 1.5 gm % and for deoxyhemoglobin to produce is > 5 gm%. Like Methemoglobinemia, Sulfhemoglobinemia is also diagnosed by spectrophotometer or gas chromatography. No specific treatment is available as sulfur binds to heme irreversibly and levels will fall only with the death of the affected RBCs<sup>4</sup>.

### Acquired Globin disorders

Here we discuss about 2 acquired alpha thalassemias namely Alpha Thalassemia with Mental Retardation (ATR) and Alpha Thalassemia associated with Myelodysplastic Syndrome (ATMDS)

### Introduction to Thalassemia

Thalassemias are genetic disorders occurring due to deficiency of globin chains and are generally inherited. Alpha thalassemia occurs due to deficiency or absence of alpha chains & beta thalassemia occurs due to deficiency or absence of beta globin chains. 4 genes in chromosome 16 control the production of the 2 alpha chains of which 2 genes are from maternal side and 2 from paternal side. Also, of the 2 genes in chromosome 11 which control the production of the 2 beta chains, 1 gene comes from each parent.

Beta thalassemias are of 2 types - beta thalassemia major (when both beta genes are affected) and beta thalassemia minor (when one beta gene is affected). Alpha thalassemias are of 4 types. When 1 of the 4 alpha genes is affected it is called  $\alpha^+$  thalassemia, when 2 alpha genes are affected it is called  $\alpha\alpha$  thalassemia. When 3 alpha genes are affected its HbH disease and when all 4 alpha genes are affected it is called Hb Bart's. In Hb H, the remaining globin chains are beta while in Hb Bart's, all 4 globin chains are  $\gamma$  type ( $\gamma$  tetramer) and  $\gamma$  chains have high affinity for oxygen and so fetus develops hypoxia, hydrops fetalis occurs and the condition is incompatible with life. All these thalassemias are congenital.

### Acquired Alpha Thalassemia (also called acquired Hb H disease)

While thalassemias are nearly always inherited, it can also be rarely acquired. Most of the acquired alpha thalassemia develops in patients with Myelodysplastic syndrome (MDS) and a few have been reported in patients with aplastic anemia. Such acquired mutations can occur in the alpha gene clusters or other in the regulatory genes which control the expression of alpha globin chains. 2 regulator genes have been found, one called HS - 40 (Hypersensitive Site - 40), present in the same chromosome 16 as alpha globin gene clusters but present more upstream and the other ATRX gene (Alpha Thalassemia mental Retardation X - linked gene) present in the X chromosome<sup>5</sup>.

### Alpha Thalassemia associated with Mental Retardation (ATR)

This occurs due to an acquired mutation in ATR - 16 gene (mutation in chromosome 16) or in ATR - X gene (mutation in X chromosome)<sup>6</sup>. The affected children with any of these 2 mutations have alpha thalassemia with mental retardation and facial abnormalities. ATR - X gene phenotype are all male. They might also have cardiac, renal, skeletal and genital abnormalities<sup>6</sup>.

### Alpha thalassemia associated with Myelodysplastic Syndrome (ATMDS)

This also occurs due to mutation in ATRX gene. Certain MDS patients develop this mutation causing alpha thalassemia. When alpha thalassemia develops in MDS

patients, the usual peripheral smear picture of MDS changes from predominantly macrocytic RBC to microcytic hypochromic RBC<sup>7</sup>. In addition HbH inclusions also develop within RBCs. As mutation is in ATR- X gene, these MDS patients are mostly Males and their median age of onset is 68 years. When MDS transforms into leukemia these thalassemic RBCs disappear.

### Conclusion

Few diseases which we think can only be congenital, can also occur be acquired. Site of mutation can be different but the phenotype resembles the inherited ones. Among the acquired globin disorder, alpha thalassemia is well characterised and its occurrence with MDS is well documented.

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