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—【Review】—総　説—

# Hemoglobinopathies

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## Introduction

Red blood cells (RBCs) contain near-saturated hemoglobin (Hb), which binds oxygen in the alveoli and transports it to tissues. Carbon dioxide ($CO_2$) emitted from tissues is taken up by RBCs and then biochemically processed. When the Hb concentration in the blood is low, the oxygen-carrying capacity of RBCs is reduced, rendering tissues hypoxic and inducing symptoms such as exertional dyspnea and general malaise.

Hemoglobinopathies can be broadly divided into thalassemia and abnormal hemoglobinopathy. The pathogenesis of thalassemia is attributable to the quantitative imbalance of α- and β-hemoglobin chains, resulting in peroxidation of lipids and proteins in RBCs by reactive oxygen species produced by free heme released from the excess hemoglobin chain[1]. Conversely, in unstable hemoglobinopathy, the hemoglobin chain is destabilized due to a change in the amino acid sequence of the globin chain, resulting in damage to lipids and proteins in RBCs[2]. Both thalassemia and unstable hemoglobinopathies result in a shortened RBC lifespan and are categorized as congenital hemolytic anemias, but clinicians sometimes encounter hemoglobinopathy without hemolysis. This review outlines the relationship between hemoglobinopathy and abnormally low values in percutaneous arterial oxygen saturation, abnormally low levels of HbA1c in subjects with glucose intolerance, and high levels of methemoglobin without certain pathological conditions.

## Thalassemia and unstable hemoglobinopathy

The etiology of anemia includes conditions such as bleeding, myelosuppression, hemolysis, and ineffective erythropoiesis[3]. Hb is a heterotetramer composed of two α-globin and two non-α-globin chains with one heme molecule bound to each globin. The site of hematopoiesis changes from the yolk sac at the embryonic stage to the fetal liver at the fetal stage and finally to the bone marrow at the adult stage[3]. The α-globin locus, located on chromosome 16, contains the α1 and α2 genes, and the β-globin locus, on chromosome 11, contains the Gγ, Aγ, δ, and β loci. Globin gene expression changes sequentially according to developmental stage, with composition of the major hemoglobin tetramer changing from α2γ2 in the fetal period to α2β2 in adulthood[3].

α-thalassemia develops when a gene deletion occurs in a flanking region, including the α-globin locus, α1 and α2. β-thalassemia is mainly caused by a missense mutation (single amino acid substitution) in the β-globin gene[4]. Fig. 1 illustrates the fate of β-hemoglobin and α-hemoglobin, which are in excess in α-and β-thalassemia, respectively. The excess β-hemoglobin in α-thalassemia forms a homotetramer (β4) in RBCs[5]. Although β4 does not have oxygen-carrying capacity, it is relatively stable in RBCs as compared with the α-hemoglobin monomer, and the generation of reactive oxygen species due to the release of heme is low. Conversely, excess α-hemoglobin in β-thalassemia cannot form a tetramer; hence, heme is easily released and lipids and proteins in RBCs are easily peroxidized[5].

The prevalence of thalassemia carriers in Japan is 1 in 3,000-5,000, with β-thalassemia carriers numbering 1 in 700-1,000, and α-thalassemia carriers approximately 1 in 5,000[6]. A type of mutation called the Southeast Asian (SEA) type deletion has been identified in half of Japanese α-thalassemia carriers[6]. The SEA type lacks a sequence of approximately 20 kb containing α-

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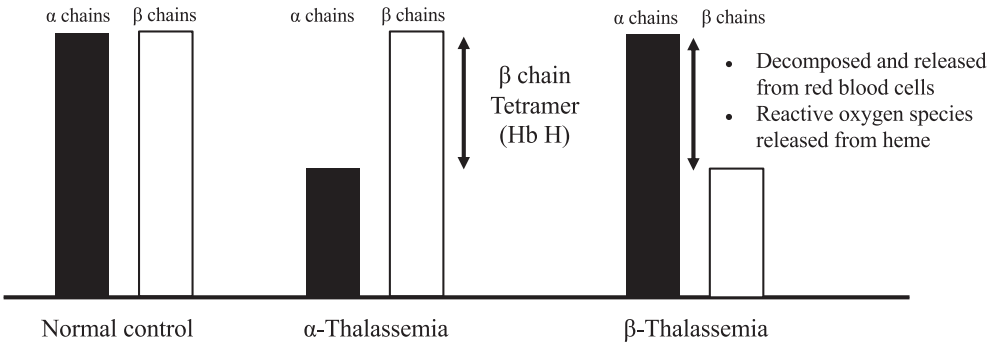


Fig. 1 Etiology of α-/β-thalassemia

globin genes (*HBA1* and *HBA2*). Hb levels are usually toward the lower limit of normal, and the RBCs are microcytic. This type is rarely accompanied by anemia symptoms[7]. Conversely, in β-thalassemia, there are many point mutations in the β-globin gene (*HBB*). In the case of Japanese individuals with thalassemia, the etiology can be determined in approximately 80% of cases by examining the eight types of gene mutation[4].

Since thalassemia presents with microcytic anemia, mild cases found in clinical practice in Japan may be treated as "erythrocytosis" or "polycythemia" due to an increase in the number of RBCs. Moreover, since iron deficiency anemia, the most common etiology of anemia, also presents with microcytic anemia, a diagnostic workup to rule out iron deficiency may be necessary. Table 1 presents the diagnosis of different etiologies of microcytic anemia using the Mentzer index[8]. The Mentzer index is an index that can be easily calculated from blood count data. One advantage is that it can be used to roughly distinguish among possible diagnoses without patients having to wait for test results for serum iron, ferritin, and transferrin saturation at the time of the first outpatient visit. However, those biochemical data are essential for a definitive diagnosis.

If the calculated result using MCV (*fl*) and RBC count (10e6 /*μl*) is <13, thalassemia is suspected; if it is ≥13, other etiologies such as iron deficiency anemia should be considered. Since thalassemia not only shortens the lifespan of mature RBCs but also involves ineffective erythropoiesis[9], erythropoiesis in the bone marrow is promoted; consequently, the number of RBCs often exceeds the reference value, and a low Mentzer index value is obtained.

Table 2 summarizes the blood count data, Hb, Mentzer index, HbF, HbA2, and genetic test results of patients with thalassemia and Hb abnormalities experienced in our department. All 10 patients with MCV < 70 had a Mentzer index of <13, but one had α-chain hemoglobinopathy and Hb Constant Spring[10]. Both HbF and HbA2 showed high values in five cases of β-thalassemia and reference values in four cases of α-thalassemia. Of the seven hemoglobinopathy cases, Hb Cheverly[11] and Hb Koln[12] are unstable hemoglobinopathies with chronic hemolytic anemia and acute hemolytic crises, and Hb Rothschild[13] and HbM-Saskatoon[14] are consulted because of cyanosis and abnormally low $SpO_2$ levels.

Table 1 Mentzer index

| |
|---|
| MCV (*fl*) /RBC count (×10e6/*μl*) |
| <13: suspect thalassemia |
| 13<: thalassemia is less likely |
| Ex.) MCV 60/RBC count 6×10e6 → index: 10 |
| MCV 75/RBC count 5×10e6 → index: 15 |

Unstable hemoglobinopathy is a type of congenital hemolytic anemia characterized by the tendency to experience acute hemolytic attacks against a background of chronic hemolytic anemia. When unstable Hb denatures and precipitates in RBCs, structures called Heinz bodies appear in RBCs[15]. In severe cases of hemoglobinopathies, RBC deformability is impaired by Heinz bodies, and a part of the RBC membrane is lost together with Heinz bodies in the reticuloendothelial system. Additionally, poikilocytes and schistocytes are observed, similar to those seen in hemolytic anemia caused by microangiopathy[16]. Screening using the isopropanol instability test[17] is useful, though a definitive diagnosis is made by genetic testing (Table 3). In a 1999 epidemiological survey, unstable hemoglobinopathy accounted for 0.8% of the etiologies of congenital hemolytic anemias, less frequent than hereditary spherocytosis (71%), erythroenzymopathy (5.9%), and thalas-

Table 2　Mentzer indices, HbF and HbA2 values in thalassemia and structural hemoglobinopathies in our department

| MCV (fl) | RBC ($\times 10^6$) | Hb (g/dl) | Mentzer index | HbF (%) | HbA2 (%) | Diagnosis |
|---|---|---|---|---|---|---|
| 52.1 | 5.30 | 8.0 | 9.8* | **6.6** | 1.7 | Hb Constant Spring |
| 59.7 | 5.88 | 11.7 | 10.2* | **8.4** | **4.8** | $\beta^0$ thalassemia |
| 60.0 | 5.95 | 12.0 | 10.1* | **8.3** | **4.8** | $\beta^0$ thalassemia |
| 61.0 | 6.74 | 13.6 | 9.1* | **2.9** | **6.4** | $\beta^0$ thalassemia |
| 61.0 | 7.37 | 12.9 | 8.3* | 0.3 | 2.4 | α thalassemia |
| 61.5 | 6.65 | 12.9 | 9.2* | 0.4 | 2.7 | α thalassemia |
| 65.0 | 4.88 | 10.1 | 13.3 | 0.6 | 2.7 | α thalassemia |
| 66.0 | 5.46 | 11.7 | 12.1* | **3.5** | **4.9** | $\beta^0$ thalassemia |
| 66.4 | 4.55 | 9.6 | 14.6 | **3.5** | **4.8** | $\beta^0$ thalassemia |
| 68.7 | 5.91 | 13.5 | 11.6* | 0.6 | 2.0 | α thalassemia |
| 81.0 | 4.78 | 12.5 | 16.9 | **3.4** | 2.2 | Hb Rothschild |
| 81.4 | 3.65 | 9.6 | 22.3 | **19.3** | 2.2 | HbM-Saskatoon |
| 82.8 | 3.14 | 8.2 | 26.4 | **15.9** | 1.6 | HbS |
| 85.0 | 5.07 | 14.3 | 16.8 | 0.8 | 3.0 | Hb Cheverly |
| 93.8 | 3.52 | 9.8 | 26.6 | **2.6** | 2.8 | Hb Koln |
| 95.0 | 3.77 | 10.6 | 25.2 | **4.1** | **4.4** | Hb Koln |
| 99.0 | 3.99 | 13.0 | 24.8 | 0.7 | 3.0 | HbM-Saskatoon |

*Mentzer index＜13
In some cases, the etiology cannot be determined without globin gene analysis.

Table 3　Clinical characteristics of unstable hemoglobinopathies

- Congenital hemolytic anemia due to autosomal dominant inheritance or de novo mutation
- Homozygotes are lethal
- Hb denatures and precipitates in erythrocytes
- Hemolytic attacks occur after infection, stress or medication
- Screening test: Isopropanol instability test

semia (3.5%)[18].

Sickle cell disease (SCD) is a type of structural hemoglobinopathy. In a hypoxic environment, abnormal hemoglobin crystallizes in RBCs, causing the RBC to deform into a sickle shape. This can produce episodes of pain due to vascular occlusion and multi-organ dysfunction due to circulatory disorders[19].

**Observation of abnormally low value of arterial oxygen saturation ($SpO_2$) on pulse oximetry**

The pulse oximeter, widely used as a point-of-care testing device, calculates arterial oxygen saturation using two wavelengths, 660 and 940 nm; oxyhemoglobin transmits red light at 660 nm, and deoxyhemoglobin absorbs it. Since Hb Bonn, a type of abnormal Hb, absorbs red light at 660 nm even in the oxygenated state, an abnormally low $SpO_2$ value is observed in pulse oximetry using the two wavelengths[20]. Fig. 2 depicts a diagnostic flowchart for when an abnormal decrease in $SpO_2$ is observed in the absence of any respiratory or circulatory disorders[21]. First, $SaO_2$ and methemoglobin levels are measured by arterial blood sampling to confirm the existence of true hypoxemia. If the $SaO_2$ is normal, qualitative abnormalities in Hb are examined by Hb isoelectric focusing, and Hb genetic testing may be performed if necessary[21].

**Discrepancy between fasting blood glucose and HbA1c levels**

Glycated Hb/glycohemoglobin is a state in which hemoglobin A (HbA) is non-enzymatically bound to glucose. Its level does not fluctuate due to physiological factors compared to the blood glucose level and urinary sugar level, which are easily affected by dietary content, exercise duration, and stress. The ratio of glycated hemoglobin to hemoglobin is an important indicator in assessing diabetes since it is considered to reflect the average blood glucose levels over the past 3 months[22].

Maintaining HbA1c levels below 7% is associated with a reduced risk of diabetic complications in patients with type 2 diabetes requiring medication. Table 4 presents some cases in which HbA1c did not reflect long-term average blood glucose levels[22]. In cases of hemolytic anemia due to shortened RBC lifespan, HbA1c levels decrease due to the early death of RBCs containing glycated hemoglobin, with a relative increase in reticulocytes compared to immature RBCs during the recovery period from blood loss. In anemia caused by a deficiency of nutrients required for

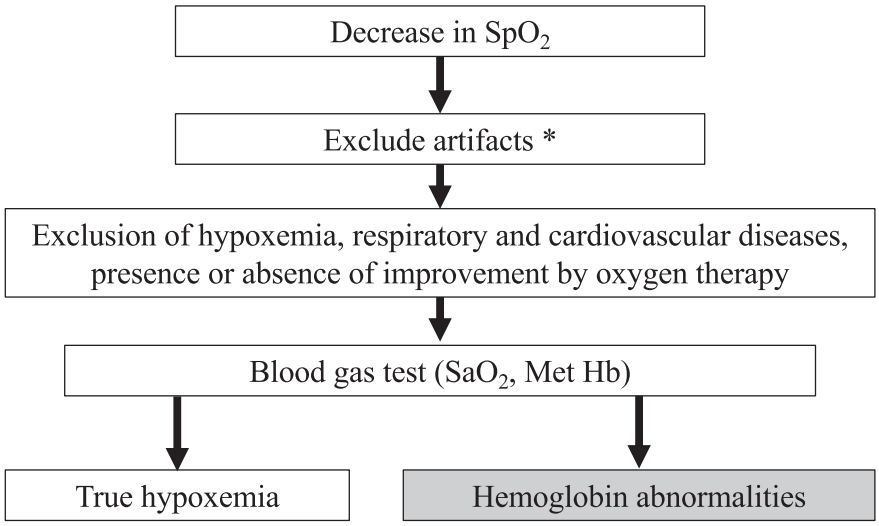


Fig. 2 Low $SpO_2$ associated with abnormal Hb

Table 4 Case of false low-HbA1c values

| |
|---|
| 1) A pathological condition in which the average red blood cell lifespan is shortened |
| ➢ Hemolytic anemia |
| ➢ Recovery period from acute blood loss |
| ➢ Renal anemia during erythropoietin administration |
| ➢ Megaloblastic anemia during vitamin B12 and folic acid supplementation |
| ➢ Hypersplenism |
| 2) Abnormal glycation of hemoglobin |
| ➢ Hemoglobin structural abnormality |
| ➢ Thalassemia |
| 3) others |

erythropoiesis, the reticulocyte number increases and the HbA1c level decreases during the recovery period after treatment. In contrast, cases in which HbA1c levels decrease because of an unlikely glycation reaction due to abnormal hemoglobin structure have also been reported.

As previously mentioned, simultaneous measurement of HbA1c and glycated albumin is useful for screening for hemolytic anemia because HbA1c decreases sharply due to the shortened RBC lifespan[23]. However, it is not often performed as it is not covered by insurance in Japan.

**Methemoglobinemia**

Methemoglobin (MHb) is a form of hemoglobin comprising the oxidized state ($Fe^{3+}$) of iron that cannot bind oxygen. In the human body, approximately 3% of Hb is converted to MHb per day, but due to the reduction mechanism, MHb is approximately 1% in normal human blood[24]. Iron is in an oxidized state ($Fe^{3+}$) even in abnormal Hb (HbM) with reduced oxygen affinity; in general, "hereditary methemoglobinemia" is caused by an abnormal NADH-cytochrome b5 reductase, which is involved in the reduction of Hb[25]. Another Hb reduction mechanism is mediated by reduced NADPH-methemoglobin reductase; methylene blue promotes this reaction and is, therefore, applied therapeutically[26].

According to the "Manual for Serious Side Effects and Diseases" published by the Ministry of Health, Labor and Welfare in June 2007[27], glutathione biosynthesis and reduction abnormalities that lead to a decrease in reduced glutathione levels, i.e., γ-glutamylcysteine synthetase (OMIM#230450)[28], glutathione synthase (OMIM#231900)[29], and glutathione reductase deficiencies (OMIM#618660)[30] have been reported in patients developing methemoglobinemia. Furthermore, it has been reported that oxidative agents such as salazosulfapyridine and sulfamethoxazole have a high risk of causing methemoglobinemia and acute hemolytic attacks in patients with unstable hemoglobinemia[25] since the ability to reduce MHb to Hb is impaired. Table 5 presents the classification of methemoglobinemias according to pathogenesis. The ratio of oxy-Hb to total Hb can be measured using a pulse oximeter; therefore, in the presence of MHb, the oxygen saturation measured by a pulse oximeter may be lower than that calcu-

Table 5　Pathogenesis of methemoglobinemia

| |
|---|
| Acquired |
| 1) Infectious diseases: *Escherichia coli*, *Campylobacter*, etc. |
| 2) Drug properties: Antibacterial agents, antifungal agents, anesthetics, nitric acid/nitrite, etc. |
| Hereditary |
| 1) NADH-cytochrome b5 reductase (CYB5R3) abnormality (OMIM*613213) * |
| 2) HbM disease (# 617971, # 617973) |
| 3) NADPH-meth Hb reductase abnormality (OMIM 250700) |
| 4) Cytochrome b5 deficiency (OMIM*613218) |
| 5) Others |

lated based on arterial blood gas analysis, which is called the "saturation gap"[31]. It is known that acquired methemoglobinemia due to bacterial infections, drugs, or environmental factors is more common than congenital methemoglobinemia[32]. If a patient is observed to have symptoms such as elevated MHb levels or cyanosis, careful testing with acquired causes in mind is necessary before proceeding immediately with testing for hereditary methemoglobinemia.

**Transfusion Therapy for Hemoglobinopathies**

The severe form of β-thalassemia occurs in homozygotes or compound heterozygotes and results in severe anemia and increased bone marrow hematopoiesis due to hemolysis and ineffective erythropoiesis. The onset of the disease occurs between 1 and 2 years of age, and jaundice, cholelithiasis, and splenomegaly are observed in addition to anemia. Increased bone marrow hematopoiesis leads to thickening of the skull and prominence of the zygomatic arches, resulting in a so-called thalassemic facial appearance[33]. Disorders of the long bones can cause pathological fractures and growth retardation.

Homozygous β-thalassemia is classified into two groups: transfusion-dependent thalassemia (TDT), which requires regular blood transfusions from infancy to sustain life, and non-transfusion-dependent thalassemia (NTDT), which is a moderate hemolytic anemia with maintained hemoglobin (Hb) levels not requiring transfusions[33][34]. Once an infant has been diagnosed with β-thalassemia, close monitoring is needed for clinical signs that indicate the need for initiation of regular blood transfusions, which usually start at 3 months of age. Hb levels should be checked at least once a month. The indications for routine blood transfusion are severe anemia of $<7$ g/d*l* on two occasions at 1-2 week intervals and after ruling out infectious and other causes[36]. If signs of extramedullary hematopoiesis such as splenomegaly or craniofacial bone changes are observed, transfusion should be initiated regardless of Hb level[34]. An Hb level of 9-10.5 g/d*l* is recommended as a trough value before transfusion[35].

SCD is a monogenic disease that develops as a result of the substitution of the sixth glutamic acid in the β-globin gene with valine (HbS; p. Glu6Val). Under hypoxic conditions, the deoxygenated state of HbS forms a polymer in RBCs, which deform into sickle-shaped cells that occlude capillaries and can form thrombi. Ischemia occurs due to vascular occlusion caused by a thrombus, causing episodes of pain (sickle cell crisis) in the limbs and chest. Homozygotes (HbSS) exhibit serious symptoms, such as anemia, feeding disorders, splenomegaly, and recurrent infections within the first 2 years of life. In addition, vascular occlusion can cause cerebral infarction that may be associated with developmental delay[19], acute chest syndrome, leg ulcers, and aseptic necrosis of bone.

In children with SCD, annual transcranial Doppler (TCD) ultrasound assessment is recommended starting at 2 years of age, and children with cerebral blood flow velocities of 200 cm/s or higher require regular blood transfusions aimed at maintaining HbS below 30%[36]. Routine blood transfusions should be continued in childhood because discontinuation of transfusion may result in a return to high TCD velocity or the development of an apparent stroke[37]. On the other hand, the efficacy of TCD has not been confirmed in adult patients with SCD, and the efficacy of blood transfusion for primary stroke prevention is unknown; nevertheless, long-term transfusion to maintain HbS below 30% is recommended to prevent recurrent stroke[38].

Excess iron that has entered the body through long-term blood transfusion becomes deposited in the liver, kidneys, heart, and endocrine organs. As a result, hepatic fibrosis, cirrhosis, and chronic kidney damage develop, and iron deposition in pancreatic beta cells can lead to the development of diabetes mellitus and pituitary hypofunction. Eventually, congestive heart failure and fatal arrhythmias develop. Iron overload is also thought to induce disorders of the hematopoietic system other than erythrocytes[39]. In patients with a serum ferritin level of ≥1,000 ng/m*l*, or an erythrocyte transfusion volume of ≥40 units, treatment of iron overload with iron chelators need to be considered[40]. Daily administration of deferoxamine mesylate to patients

Table 6 Therapeutic agents for sickle cell disease (SCD)

| |
|---|
| 1) Hydroxyurea<br>Although it is a therapeutic drug for myeloproliferative disorders, it suppresses crystallization of HbS by promoting the production of HbF in erythrocytes of SCD patients. |
| 2) L-Glutamine<br>Glutamine is a glutathione precursor and has been approved by the FDA for the treatment of SCD. |
| 3) Crizanlizumab<br>Inhibits P-selectins, which cause multicellular interactions that lead to vascular occlusion. |
| 4) Voxelotor<br>Suppresses crystallization of HbS by increasing the oxygen affinity of Hb. |

with post-transfusion iron overload results in lower serum ferritin levels, and improved cardiac function as well as improved hematopoietic status and reduced transfusion requirements at the cost of mild liver dysfunction. It has also been shown that survival is prolonged when iron chelation therapy is appropriately administered, and iron overload may have a significant effect on prognosis[41]. However, this treatment requires intramuscular or intravenous administration, which is time-consuming for the patient and results in a high rate of noncompliance[41]. Recently, an oral iron chelator, deferasirox (Exjade/Jadenu, Novartis, Inc. Basel, Switzerland), has been developed, making practical iron chelation therapy possible[42].

## New Therapeutic Agents for Hemoglobinopathies

Luspatercept, a fusion protein, binds to the ligand for the activin receptor, a member of the transforming growth factor-β (TGF-β) superfamily, and blocks SMAD-2/3 signaling to promote red blood cell maturation[43]. A phase III study in adult β-thalassemia patients requiring regular transfusions found that it contributed to a reduction in transfusion volume and lowered serum ferritin levels[44]. Luspatercept has been approved in the United States and Europe for the treatment of anemia in adult patients with β-thalassemia requiring regular transfusions[45][46].

Table 6 presents recently developed treatments for SCD. Hydroxyurea pharmacologically reactivates fetal globin gene expression[47]. Although it was originally employed for myeloproliferative disorders, it can increase γ-globin gene expression in RBCs in patients with SCD and promote HbF production. Since maintaining the reduced glutathione concentration in RBCs contributes to HbS stabilization, oral ingestion of large amounts of L-glutamine as a glutathione precursor[48] has been established as a therapeutic method. Furthermore, crizanlizumab[49], an antibody drug that inhibits P-selectin, exerts a therapeutic effect by inhibiting multicellular interaction by P-selectin and preventing vascular occlusion. Finally, voxelotor[50] is an oral drug that increases the oxygen affinity of Hb by translocating from the blood into RBCs and suppressing HbS polymerization. Taken together, various therapeutic agents for beta-thalassemia and SCD have been developed and approved, and further clinical applications are expected.

Conflict of Interest Statement

All authors declare that they have no conflict of interest.

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# ヘモグロビン異常症

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**要旨：**

赤血球内に存在するヘモグロビンは，肺胞で酸素を結合して組織に運搬する．ヘモグロビンの異常により酸素運搬能が低下すると，組織は低酸素状態となり労作時呼吸困難や全身倦怠感などの症状が出現する．ヘモグロビン異常症はサラセミアと異常ヘモグロビン症に大別され，サラセミアはグロビン遺伝子の異常により α-および β-ヘモグロビン鎖の量的アンバランスが生じた結果発症し，鉄欠乏性貧血などとの鑑別には Mentzer index が有用である．不安定ヘモグロビン症はグロビン鎖のアミノ酸配列が変化してヘモグロビン鎖が不安定になり発症し，メトヘモグロビン血症は Hb の還元に関与する酵素の異常により発症する．また，パルスオキシメーターによる経皮的動脈血酸素飽和度測定における異常低値を示す場合，空腹時血糖が異常高値であるにもかかわらず HbA1c が低値を示す場合，メトヘモグロビンが高値を呈する場合などはヘモグロビン異常症を疑う必要がある．重症型のヘモグロビン異常症では定期的な輸血が必須であるが，輸血による鉄過剰が問題となる．β サラセミアや鎌状赤血球症では，近年様々な治療薬が開発されてきており，更なる臨床応用が期待される．

**キーワード：**
サラセミア，不安定ヘモグロビン症，メトヘモグロビン血症，鎌状赤血球症

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