Clinical Classification, Screening and Diagnosis for Thalassemia

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KEYWORDS

- Transfusion-dependent thalassemia (TDT)
- Non–transfusion-dependent thalassemia (NTDT) • Diagnosis • Screening

KEY POINTS

- Diagnosis of thalassemia and hemoglobinopathies requires a comprehensive evaluation combining red blood cell phenotypes, hemoglobin profiles, and DNA analysis.
- A recent classification of thalassemia syndrome is based on the patients' clinical severity that is their transfusion requirement, not genotypes.
- Hemoglobin analysis can be performed at any age; however, interpretation requires age-specific reference ranges.
- Genetic analysis for globin mutations are required to confirm the clinical diagnosis and are indispensable for genetic counseling, genetic risk calculation, prenatal, and preimplantation genetic testing.

INTRODUCTION

Over the past decade, our knowledge of the clinical diagnosis and management of thalassemia has progressed extensively. In recent years, the most critical change in clinical diagnosis is a new classification that has been simplified and help guiding clinical management from thalassemia intermedia (TI) into non–transfusion-dependent thalassemia (NTDT) and thalassemia major (TM) into transfusion-dependent thalassemia (TDT) based on their requirement of regular blood transfusions to survive. This new classification has included several other forms of thalassemia syndromes beside β-thalassemia diseases (β-TI and β-TM) that have been a prototype of

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thalassemia syndromes for many years. In addition, the medical technology for screening and definitively diagnosing thalassemia traits and diseases has also been improved and are the subjects of our review in this article. However, the classification of thalassemia continues to rely on clinical presentation and severity. Diagnostic tests, including molecular analyses, can only guide but not yet replace clinical evaluation and judgment.

CLINICAL CLASSIFICATION OF THALASSEMIA

Disorders of hemoglobin (Hb) are characterized according to pathologic defects on globin chain production; a quantitative defect or "thalassemia," mainly α-thalassemia and β-thalassemia, and a qualitative defect, namely hemoglobinopathy (or structural Hb variants), and, last, hereditary persistence of fetal Hb. Interactions of these 3 types of globin defects result in a wide array of thalassemia syndromes and related diseases.[1]

Thalassemia has a wide spectrum of clinical severity, which was previously used for a clinical classification of thalassemia into TM, TI, and thalassemia minor. The term TM describes patients who have severe anemia presenting early in life and requiring lifelong blood transfusions and iron chelation, whereas thalassemia minor, at the other end of clinical spectrum, are persons with asymptomatic, mild anemia and a heterozygous condition (trait) of thalassemia. The latter group requires no transfusion, but genetic counseling. TI are highly diverse group of patients with various clinical severities from mild, moderate, to moderately severe anemia, requiring no blood transfusions to occasional and frequent blood transfusions. Moreover, these clinical entities are dynamic; patients with TI particularly might require more frequent or even regular transfusions if they develop several complications owing to thalassemia, such as pulmonary hypertension, extramedullary hematopoietic masses, or chronic ulceration. In addition, early published articles and guidelines addressed mainly the clinical management and complications of TM (mostly homozygous β-thalassemia or β-TM).[2] This classification has left out several clinical thalassemia syndromes, especially α-thalassemia and the hemoglobinopathies, such as Hb E/β-thalassemia.

Recently, a concept of clinical diagnosis of thalassemia syndromes has changed dramatically owing to several clinical research and observational findings focusing on the clinical management and complications of TI showing that, even they were called a milder group according to the degree of anemia and transfusion requirement, patients with TI could develop serious complications later in their lives. Better monitoring and treatment with better outcomes are increasingly important.[3] In 2012, the new terminology for a clinical classification of thalassemia (TDT and NTDT) was proposed and then adopted by the Thalassemia International Federation in their recent guidelines and publications.[4,5] Differentiation of a new thalassemia patient as either TDT or NTDT requires a careful clinical evaluation using several clinical and hematological parameters, particularly baseline Hb levels (**Fig. 1**). Most patients with β-TM and those who have survived Hb Bart's hydrops have a very severe phenotype and could be easily classified as TDT. However, in patients with other thalassemia syndromes, particularly Hb E/β-thalassemia, usually present during an intercurrent infection that is causing an acute hemolytic crisis that can make their presentation to be more serious, with an enlarged spleen and a low Hb level with symptomatic anemia.[6] It is recommended to follow such patients for at least 3 to 6 months to observe their clinical severity at their true baseline before a diagnosis of TDT or NTDT is made.