Clinical Complications and Their Management

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KEYWORDS

• Thalassemia • Ineffective erythropoiesis • Iron overload • Heart failure
• Liver disease • Endocrinopathies

KEY POINTS

- Thalassemia syndromes, clinically speaking, include transfusion-dependent and non–transfusion dependent forms.
- Ineffective erythropoiesis, chronic hemolytic anemia, compensatory hemopoietic expansion, hypercoagulability, and increased intestinal iron absorption are the hallmarks of thalassemias due to the α/β globin chain imbalance and are responsible for several clinical complications.
- Iron overload, secondary to increased iron absorption and to blood transfusions, causes organ damage.
- Treatment of anemia and iron overload may prevent clinical complications.
- In patients with thalassemia standard management for specific morbidities, beyond transfusion and iron chelation, should be considered.

INTRODUCTION

Clinical complications in thalassemias are systemic, and they are the consequence of the underlying pathophysiologic mechanisms, namely, ineffective erythropoiesis, chronic hemolytic anemia, compensatory hemopoietic expansion, and increased intestinal iron absorption. In the severe forms clinical complications can be the consequence of the treatment with red blood cell transfusions, which lead to iron overload. Nevertheless some complications are present similarly in patients with transfusion-dependent thalassemia (TDT) and in patients with non-TDT (NTDT), while some others

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can be more prevalent in one or the other form.[1] In this review we discuss the most clinically relevant complications, comparing the presentation and the characteristics in TDT and in NTDT (Table 1 and Fig. 1).

CARDIAC COMPLICATIONS

Cardiac Dysfunction

Despite great improvement in the clinical management of thalassemia, cardiovascular involvement represents a well-known complication and remains the primary cause of mortality in TDT and less frequently contributes to morbidity in patients with NTDT.[2,3]

The two forms of the disease have common basic underlying pathophysiologic mechanisms that affect the heart in a different extent.

In TDT, cardiac iron overload is mainly due to blood transfusions, whereas, in NTDT, iron accumulates to a lesser extent in the heart because it is due to increased intestinal iron absorption and accumulates mainly in the liver. In TDT, the heart failure due to accumulation of iron within myocytes is a major risk of death. Cardiac iron deposition occurs mainly in the ventricle, with greater accumulation in the epicardium. Moreover, free labile iron interacts with calcium channels and leads to impaired myocardial contractility.[4–6]

Patients with considerable myocardial iron overload may remain free of symptoms for a long time; once myocardial dysfunction develops, symptoms are related to the degree of ventricular impairment. In more advanced stages, clinical presentations are equivalent to those seen with any severe heart failure and may include dyspnea, peripheral edema, hepatic congestion, and severe exercise limitation. It is important to underline that iron overload complications, even when severe, may be reversed by intensive chelation therapy.

In NTDT, the heart involvement may be due to other cardiovascular causes than iron overload, such as pulmonary hypertension (PH) and thrombosis (see Hypercoagulability and Vascular Disease).

A mechanism of heart dysfunction, which is common to TDT and NTDT, is represented by an increased workload on the heart; in NTDT, because of chronic anemia,

Table 1
The difference in complications between transfusion-dependent thalassemia and non–transfusion-dependent thalassemia

Complications	TDT	NTDT	Management
Cardiac dysfunction	+++	+	Iron chelation + standard care
Arrhythmias	+	++	Standard care
Viral hepatitis	+++	+	HBV vaccination, antiviral therapy
Hepatic fibrosis, cirrhosis, and cancer	++	+++	Standard care
Growth retardation Sexual development	++	+	Transfusion + chelation + hormones
Glucose intolerance/diabetes	++	+	Standard care
Bone disease	++	+++	Standard care + specific therapy
Extramedullary hematopoietic masses	+	+++	Hypertransfusion, HU, radiation
Thrombosis	+	+++	Anticoagulation, transfusion
Pulmonary hypertension	+	+++	Standard care, sildenafil, bosentan
Leg ulcers	+	++	Topic measures, HU

Abbreviations: HBV, hepatitis B virus; HU, hydroxyurea.