About non-transfusion-dependent thalassemia (NTDT) syndromes
*The most common form of thalassemia, causing debilitating health complications, including iron overload, that can be severe and life-altering*

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<th>Understanding non-transfusion-dependent thalassemia (NTDT) syndromes</th>
<th>Non-transfusion-dependent thalassemia (NTDT) syndromes encompass several types of thalassemia, a diverse family of genetic disorders affecting red blood cell production, causing anemia. NTDT syndromes are the most common type of thalassemia among those born with the disease.¹ Unlike patients with other types of thalassemia, those with NTDT syndromes can live without regular blood transfusions, a significant cause of iron overload. Even without transfusions, NTDT patients still accumulate excess iron through intestinal absorption, leading to debilitating health complications that can be severe and life-altering.² Because NTDT patients are not symptomatic at birth, when most thalassemias are diagnosed, they are often underdiagnosed and undertreated.³ Diagnosis of NTDT syndromes can be confirmed with blood tests and genetic testing that may affect prognosis and management of the condition.⁴</th>
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| Types of NTDT syndromes | NTDT syndromes occur in three major genetic types of thalassemia:⁵
- **Beta-thalassemia intermedia (TI)** is common in people of Mediterranean and Middle Eastern descent.⁶ The disease may present between the ages of 2 and 6 and most patients do not need regular blood transfusions to manage their condition.⁶
- **Hemoglobin H disease (HbH-alpha-thalassemia)** is predominantly seen in people of Southeast Asian, Middle Eastern and Mediterranean descent.⁷
- **Hemoglobin E-beta-thalassemia** occurs predominantly in people of South and Southeast Asian descent.⁸ The severity can vary significantly, with some patients experiencing no symptoms and others requiring regular transfusions.⁸ |
| Prevalence of NTDT syndromes | According to published studies, at least three quarters of a million people worldwide have NTDT syndromes, although as understanding of the disease increases, it is probable the number will grow.⁸⁻¹⁰ Most NTDT patients are of South and Southeast Asian, Mediterranean or Middle Eastern origin, with immigration broadening the global prevalence.¹ |
| Clinical complications of NTDT syndromes | Some clinical complications are more common in NTDT patients than in transfusion-dependent thalassemia patients and can vary significantly based on the severity of the disease. Complications often increase with age and can include:¹¹
- Overproduction of red blood cells inside and outside of the bone marrow, called extramedullary hematopoiesis
- Leg ulcers
- Heart disease
- Cholelithiasis (gallstones)
- Abnormal liver function
- Diabetes |
### Iron overload in NTDT patients

Although they do not require regular blood transfusions, patients with NTDT syndromes can develop iron overload as a result of excessive absorption of iron in the gastrointestinal tract. Despite a slower rate of iron accumulation, the burden of iron overload in NTDT patients is similar to that observed in thalassemia patients who receive regular blood transfusions.

In NTDT patients, accumulation of excess iron in the body is associated with an increased risk of serious complications. Many symptoms begin to appear as early as age 10 and become increasingly common as patients reach their 20s and 30s. These complications include:
- Blood clots
- Bone disease (including osteoporosis)
- Pulmonary hypertension
- Endocrine diseases, including:
  - Hypothyroidism
  - Hypogonadism
- Liver fibrosis and cirrhosis (can be indicated by abnormal liver function)

### Treatment of NTDT syndromes and iron overload

Management of NTDT syndromes varies greatly depending on the clinical complications experienced by individual patients and the level of iron overload. The three main courses of treatment for NTDT patients include:

- **Transfusion therapy:** Some patients with NTDT syndromes may receive blood transfusions to help fight infections and for other reasons. However, these transfusions can increase the risk of iron overload.
- **Iron chelation therapy:** The administration of chelating agents to remove iron from the body.
- **Splenectomy:** In NTDT patients, the size of the spleen can increase over time, resulting in worsening anemia and the need for more transfusions. Splenectomy (removal of the spleen) can reverse these effects, but carries the risk of serious complications including blood clots, pulmonary hypertension and silent stroke.

### Monitoring iron overload in NTDT patients

When blood transfusion is initiated in patients with NTDT, they require close monitoring of iron in the body. Patients having sustained frequent transfusions for extended periods of time may be tested every 3-6 months for elevated iron levels. Chelation therapy may be introduced and then withdrawn once the desired outcomes are achieved and iron is at healthy levels. Iron levels in the body can be measured by two methods:

- **Serum ferritin (SF):** A noninvasive and inexpensive blood test which allows for frequent monitoring. However, SF tests are an indirect measurement of iron burden and can require several tests or combinations with other indicators of iron overload to improve accuracy.
- **Liver iron concentration (LIC):** A more accurate measurement of iron levels that tests tissues in the liver, the main site of body iron storage. Testing can be done via biopsy, magnetic resonance imaging (MRI), or a superconducting quantum interference device (SQUID).
References