NON-TRANSFUSION-DEPENDENT THALASSAEMIA: A PANORAMIC SURVEY FROM PATHOPHYSIOLOGY TO TREATMENT

Abdul-Hamid A. Bazarbachi,1 Bachar F. Chaya,1
Hassan M. Moukhadder,2 *Ali T. Taher2

1. Faculty of Medicine, American University of Beirut Medical Center, Beirut, Lebanon
2. Division of Hematology/Oncology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon
*Correspondence to ataher@aub.edu.lb

Disclosure: Ali T. Taher receives research funding and honoraria from Novartis Pharmaceuticals. All other authors have declared no conflicts of interest.

Received: 11.04.16 Accepted: 06.07.16
Citation: EMJ. 2016;1[4]:53-61.

ABSTRACT

Non-transfusion-dependent thalassaemia (NTDT) is a rather broad term that encompasses a group of thalassaemia syndromes, most commonly β-thalassaemia intermedia, haemoglobin E/β-thalassemia, and α-thalassaemia intermedia (haemoglobin H disease). Importantly, these entities do not require regular blood transfusions for survival, and therefore have transfusion independence. Clinical morbidities associated with the NTDTs are the end result of the culmination of three principal pathophysiological aberrancies: ineffective erythropoiesis, chronic anaemia (and associated haemolysis), and iron overload. Such complications involve multiple organs and organ systems; hence, the importance of prompt identification of at-risk individuals and holistic management of diagnosed subjects can never be overstated. Several management options, both medical and surgical, remain at the disposal of involved clinicians, with a significant body of data favouring the virtue of iron chelation therapy, fetal haemoglobin induction, and treatment with blood transfusions, the latter only when absolutely indicated, with reservation of splenectomy to a few select cases. Yet, a better understanding of the molecular phenomena at the origin of the disease process in the NTDT syndromes calls for a pressing need to explore novel therapeutic modalities, in light of the increasing incidence of NTDT in the developed world.

Keywords: Non-transfusion-dependent thalassaemia, anaemia, iron overload, complications, chelation.

INTRODUCTION

Inherited haemoglobin disorders are divided into two main groups: 1) thalassaemia α and β with defective globin chain synthesis in adult haemoglobin and 2) structural haemoglobin variants S, C, and E. Thalassaemia can be associated with a myriad of phenotypes as a result of simultaneous inheritance of two different thalassaemia mutations, one from each parent, or possibly its co-inheritance with structural haemoglobin variants. In fact, multiple classification systems have been developed to categorise the thalassaemia syndromes, but transfusion dependence probably remains the most important criterion in classifying thalassaemias and differentiating between their severities. Transfusion-dependent-thalassaemias (TDTs) constitute the more severe end of the disease spectrum and include α-thalassaemia major (TM) and β-TM. On the other hand, non-transfusion-dependent thalassaemias (NTDTs) describe patients who do not require life-long transfusions for survival, allowing that transfusions might still be required in particular clinical scenarios. The term ‘NTDT’ includes β-thalassaemia intermedia (TI), haemoglobin E/β-thalassemia, and α-TI (or haemoglobin H disease), in addition to the much rarer forms of haemoglobin S/β and C/β-thalassaemia.
EPIDEMIOLOGY

Thalassaemia constitutes a major public health burden despite its decreasing prevalence in the last few years. \(\alpha\)-thalassaemia remains the most common thalassaemia, with 1 million individuals affected by the various \(\alpha\)-thalassaemia syndromes worldwide. Whereas 5% of the world population are carriers of \(\alpha\)-thalassaemia, 1.5% (80 million) are carriers of \(\beta\)-thalassaemia, most of whom are transfusion-dependent. The difference between the prevalence of the transfusion-dependent (e.g. TM) and transfusion-independent syndromes is not clear, especially that data on the epidemiology of the latter are limited. In general however, NTDTs are especially relevant in the Sub-Saharan African and Mediterranean regions due to the high prevalence of consanguineous marriages in these parts of the world. Interestingly, a protective role against malaria acquisition has been associated with the genetic polymorphisms underlying the various thalassaemia syndromes, which might partially explain the relatively high frequency of the latter in malaria-infested areas.\(^{1,2}\)

PATHOPHYSIOLOGY AND COMPLICATIONS

The pathophysiology of NTDT, similar to that of the other thalassaemia syndromes, can be portrayed as haemoglobin chain imbalance and ensuing oxidative damage.\(^3\) The pathophysiological derangements defining NTDT are usually clustered under the all-encompassing triad of ineffective erythropoiesis (and associated compensatory extramedullary haematopoiesis), chronic anaemia and related haemolysis, and iron overload (Figure 1).\(^4\) The complications associated with NTDT are intertwined with the aforementioned triad, while other complications can be regarded

---

**Figure 1:** Pathophysiological cornerstones in non-transfusion-dependent thalassaemia and their associated complications.

NTDT: non-transfusion-dependent thalassaemia.
as subcategories of these three processes. In this section, we outline the principal complications of NTDT at the level of various organ systems.

**Blood-Related Complications**

**Iron overload**

Hepcidin is an inflammatory protein responsible for removing iron from the circulation and promoting its entrapment in macrophages and liver cells. It also decreases iron absorption from the gut and is therefore one of the main regulators of iron entry into the body. In states of abnormally low hepcidin levels in the blood, such as in NTDT, an excess of iron is absorbed by the gut with increased export from reticuloendothelial cells. The end result is an inevitable drastic increase in free iron in the circulation, which itself incites oxidative damage and brings about end-organ compromise. It is worth noting that although transfusion therapy is the main mechanism of iron overload in TDT, occasional transfusions due to complications in NTDT contribute, to a lesser extent, to the iron overload state. Similar to TDT, iron overload in NTDT is managed by chelation therapy which is only indicated in NTDT patients if iron concentrations reach threshold levels associated with increased iron-related complications. These threshold values include liver iron concentration ≥5 mg/g of dry weight, or, in the absence of liver iron concentration measurement, serum ferritin level ≥800 ng/mL in patients >10 years old (or 15 years in haemoglobin H disease).

**Hypercoagulable state**

In general, thromboembolic phenomena related to thalassaemia are 4.38-times more common in TI than in TM. The aetiology of the hypercoagulable state in the thalassaemia syndromes, and NTDT in particular, is multifactorial. Incriminated are the procoagulant activity of haemolysed circulating red blood cells and associated increased platelet activation, coagulation factor defects, depletion of antithrombotic factors, and endothelial inflammation. Splenectomy is an additional risk factor provided that one-third of the total platelets are normally sequestered in the spleen. A study by Taher et al. determined that splenectomised TI patients who experience thromboembolic events in association with a hypercoagulable state are characterised by a high nucleated red blood cell count (≥300×10^9/L) and a high platelet count (≥500×10^9/L). They are also more likely to have evidence of pulmonary hypertension and be transfusion-naïve. Nucleated red blood cells, in particular, demonstrate the presence of adhesion molecules which might contribute to the hypercoagulable state seen in patients with thalassaemia.

**Pulmonary hypertension**

Another pressing haematological complication in thalassaemics is pulmonary hypertension which is a serious condition and requires urgent intervention. Pulmonary hypertension is diagnosed when tricuspid valve regurgitant jet velocity is found to exceed 2.5–2.8 m/s, the equivalent of a pulmonary arterial systolic pressure of 30–35 mmHg. Although believed to be due to vasculopathy resulting from excessive haemolysis combined with nitric oxide depletion and enhanced platelet activation, the exact mechanism underlying the association between pulmonary hypertension and thalassaemia remains unknown. However, it was observed that nucleated red blood cells might be involved in the mechanisms accounting for pulmonary hypertension after splenectomy, possibly due to their effect on the coagulation system. Pulmonary hypertension is 5-times more prevalent in NTDT than in TM as revealed by right heart catheterisation. On the other hand, it was observed that transfusions significantly reduced pulmonary hypertension in patients with thalassaemia. This, however, needs to be reproduced in clinical trials before a definite conclusion can be drawn.

**Iron overload cardiomyopathy**

Iron overload cardiomyopathy (IOC) is a form of dilated cardiomyopathy characterised by a decrease in the left ventricular ejection fraction due to left ventricular chamber dilation. Although IOC is usually present in TDT, a NTDT-like pattern of iron overload attributable to abnormally low levels of hepcidin in the circulation is usually also present. However, data is lacking on whether IOC can be associated with NTDT, especially since cardiac iron overload is by far a less important concern in NTDT than it is in TDT.

**Other haematological complications**

Other haematological abnormalities observed in NTDT include haemolytic crises and silent brain infarcts, but these are much less prevalent than the above-mentioned disease entities and therefore will not be discussed further.
Extramedullary Haematopoiesis

As previously mentioned, one of the hallmarks of thalassaemia is ineffective erythropoiesis which entails insufficient bone marrow function. This failure to meet circulatory demands drives the body to reinitiate extramedullary haematopoiesis as a compensatory mechanism, a process normally engaged in fetal organs during gestation. This phenomenon can take place almost anywhere in the body but most commonly involves the spleen and liver which explains the hepatosplenomegaly often noted in thalassaemia patients. Also involved, though to a lesser extent, are the lymph nodes, thymus, heart, breasts, prostate, broad ligaments, kidneys, adrenal glands, pleura, retroperitoneal tissue, skin, peripheral and cranial nerves, and spinal canal. Interestingly, a recent case report by Cuttler et al. brought attention to extramedullary haematopoiesis in the conjunctiva of a myelofibrosis patient, which suggests a high index of suspicion should be maintained for extramedullary haematopoiesis in unusual anatomical locations. An especially problematic occurrence remains to be paraspinal extramedullary haematopoiesis which usually presents as pseudotumours that can cause a variety of neurological symptoms due to spinal compression. Yet 80% of cases remain asymptomatic and lesions reported in these patients are incidentally discovered on imaging studies performed for other purposes. It should be noted that extramedullary haematopoiesis is far more commonly observed in NTDT than in TDT because NTDT patients do not receive regular transfusions and usually present with chronic haemolytic anaemia.

Hepatobiliary Complications

α/β globin chain imbalance causes red blood cell instability leading to haemolysis which can in turn contribute to the formation of gallstones. Gallstones increase the risk of cholecystitis, a potentially fatal complication in splenectomised patients.

Another menacing hepatobiliary complication in NTDT is liver damage stemming from iron accumulation in the liver parenchyma. Iron deposition in the liver causes fibrosis and eventually cirrhosis, thereby increasing the risk of hepatocellular carcinoma (HCC). Furthermore, NTDT patients who eventually require blood transfusions are at risk of developing viral hepatitis which further inflates the incidence of HCC development. This has prompted the strong recommendation of vaccination against hepatitis B virus for primary prevention of hepatitis B and hepatitis B virus-related HCC, in addition to regular screening with biannual liver ultrasonography and serum α-fetoprotein levels for timely detection of high-risk lesions and apt intervention directed at tumourigenic foci.

Endocrine and Bone Disease

Endocrine gland dysfunction is a common morbidity in NTDT although its prevalence is generally higher in TM. Clinical, radiological, and biochemical studies have confirmed the correlation between iron overload and endocrine gland toxicity. Unlike skeletal deformities and growth delay, which are more commonly encountered in TM, hypothyroidism, hypoparathyroidism, adrenal insufficiency, diabetes mellitus, and hypogonadism are more prevalent in NTDT. On the other hand, although more common than in TDT, hypothyroidism, hypogonadism, and diabetes mellitus remain quite rare in NTDT. In addition, patients with TI generally have normal sexual development and are usually fertile despite the fact that they tend to experience puberty late. Importantly, the OPTIMAL CARE study concluded that iron chelation decreases the risk of such complications. Iron overload, in addition to nutritional imbalance and increased erythron (due to ineffective erythropoiesis), also explains the occurrence of osteoporosis, osteopenia, and other low bone mineral density states in NTDT patients.

Leg Ulcers

NTDT patients are at a higher risk of developing leg ulcers in comparison with regularly transfused TM patients. This risk increases with age meaning that approximately one-third of poorly treated NTDT patients will eventually develop leg ulcers. The pathophysiology of leg ulcers in NTDT can be explained by tissue fragility and eventual ulceration. The key factor in the pathogenesis of this complication is reduced tissue oxygenation, which is believed to be due to the combination of anaemia, hypercoagulability, and ineffective erythropoiesis.

Pregnancy-related Complications

Females with NTDT have a high risk of developing pregnancy complications ranging from preterm delivery to intrauterine growth restriction (IUGR)
and spontaneous abortion.\textsuperscript{40} A series by Nassar et al.,\textsuperscript{41} one of the largest of its kind for pregnant NTDT females, showed that 57.1% of pregnancies in this patient population are complicated by IUGR. It also revealed that blood transfusions during pregnancy, although potentially associated with complications, do decrease the risk of IUGR as well as other complications because anaemia is physiologically exaggerated in all pregnant women.\textsuperscript{41} In healthy pregnant females, the haemoglobin level should be kept >10 g/dL for optimal development of the fetus.\textsuperscript{42} However, according to a case series by Origa et al.\textsuperscript{40} of pregnant women with NTDT, targeting the 10 g/dL cut-off proved to be of clinical benefit to only 78% of the patients and their fetuses, where the fetuses of the other 22% ended up suffering from IUGR. This suggests that, apart from the absolute concentration of haemoglobin in the blood, transfusion therapy should be tailored to the cardiac function and general condition of the mother as well as the growth status of the fetus.\textsuperscript{40}

Another important consideration in pregnant NTDT female patients is the possible limitation of uterine enlargement by an enlarged spleen, potentially necessitating splenectomy during gestation or shortly after delivery.\textsuperscript{41,43}

Renal Complications

Renal complications in NTDT and the other thalassaemia syndromes are multifactorial in aetiology. Anaemia in and of itself affects the glomerulus by causing hyperperfusion and consequently hyperfiltration.\textsuperscript{1,44,45} Moreover, chronic hypoxia causes proximal tubular cell dysfunction which leads to interstitial fibrosis and other forms of progressive renal disease.\textsuperscript{46} Kidney function can also be compromised by the oxidative stress resulting from the iron burden. Furthermore, deferasirox, an iron chelator used by NTDT patients, has been noted to cause renal toxicity on rare occasions, which has prompted the recommendation of monthly renal function monitoring in deferasirox users.\textsuperscript{4} On a separate note, a recent report by Ricchi et al.\textsuperscript{47} on three cases of renal malignancy in TM patients highlights the tumourigenic role of hypoxia-inducible factors and of the iron-induced oxidative damage incurred by the renal parenchyma. In theory, provided that both chronic hypoxia and iron overload are also present in TI, it can be speculated that NTDT might represent a preneoplastic state at renal level, but much investigation into this matter is required before such a conclusion can be inferred.

Malignancies

In general, thalassaemia patients today are more likely to develop malignancies of several organs, especially HCC and haematological cancers, as a consequence of improved survival.\textsuperscript{48} Contributors hypothesised to be linked to the increased cancer risk in thalassaemia patients compared with the general population are iron, transfusion-transmitted viruses, transfusion-related immunosuppression, and haematopoietic drive.\textsuperscript{48} Importantly, a recent longitudinal cohort study from Taiwan reported a significantly higher risk of developing cancer in any organ in TDT than in NTDT patients, with a hazard ratio of 6.7.\textsuperscript{49} However, additional studies on cancer in thalassaemia are warranted, especially those targeting the epidemiology and pathophysiology of this rising phenomenon.

MANAGEMENT

Figure 2 illustrates the medical and surgical options available for treating NTDT patients. The treatment strategies included in the figure are discussed below.

Medical

Although restricted to those with matched donors, an allogeneically matched bone marrow transplant is potentially curative of thalassaemia.\textsuperscript{50} The therapies enlisted in this section do not cure the disease per se but rather ameliorate or nullify associated complications.

Iron chelation

In NTDT, iron chelation therapy is indicated in patients >10 years of age (or 15 years in haemoglobin H disease) if their liver iron concentration is \( \geq 5 \text{ mg/g of dry weight} \) or serum ferritin level is \( \geq 800 \text{ ng/mL} \) in the absence of liver iron concentration measurement, which have been established as thresholds associated with increased incidence of iron-related complications.\textsuperscript{6} Iron chelating drugs include agents that are given parenterally such as deferoxamine, and others that are given orally, such as deferasirox and deferasirox.\textsuperscript{51} Deferoxamine is the oldest iron chelator, and it is usually administered daily as an intravenous infusion over a period of 8 hours.\textsuperscript{51} The main limitation of this drug, however, remains poor compliance with its use due to its laborious administration method. On the other
hand, deferiprone, which is the first oral iron chelator, has a very short half-life and so is administered 3-times a day.⁵² Although effecting significant decreases in serum ferritin and non-transferrin-bound iron levels, deferiprone has been associated with adverse gastrointestinal and rheumatological events that have greatly limited its use in clinical settings.⁵³ Although reports on the detailed benefits and efficacy-to-safety ratios of deferoxamine and deferiprone in NTDT patients are still limited, the Phase II THALASSA trial by Taher et al.⁵⁴ proved the efficacy of deferasirox, which is orally administered and has a relatively long half-life, in reducing iron overload in NTDT patients. Consequently, deferasirox remains the only iron chelating agent to have been evaluated for use in NTDT and to have received US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for iron chelation in NTDT patients.⁵²

**Fetal haemoglobin inducers**

One way of correcting the α/β globin chain imbalance in NTDT is by inducing the production of fetal β-globin-like molecule, also known as γ-globin, which improves the globin chain imbalance by scavenging the excess α chains, hence increasing fetal haemoglobin (or α₂γ₂) levels and improving erythropoiesis.²,³,³³ Hydroxyurea, a well-known antineoplastic drug with both cytotoxic and antimetabolic effects, has long been used to treat anaemia associated with sickle disease. While sufficient long-term safety data has been established for its use in thalassaemia, hydroxyurea still demonstrates variable response rates where approximately 40% of NTDT patients taking the medication were found in previous studies to experience a 1 g/dL rise in serum haemoglobin.²,⁵⁵ Nonetheless, there have been reports from the OPTIMAL CARE study suggesting that hydroxyurea treatment improves various NTDT complications such as extramedullary haematopoietical tumours, leg ulcers, and quality of life.⁵⁵

Recent data support the promising role of the immunomodulator compound thalidomide in effecting a positive erythroid response in patients with NTDT, through fetal haemoglobin induction and/or by exerting its immunomodulatory effects.⁵⁶ We strongly believe this deserves to be further explored in NTDT patients in light of the phenomenal rise in haemoglobin levels observed in the two thalidomide-treated patients reported by Fozza et al.⁵⁶

**Transfusion therapy**

Although NTDT patients are by definition transfusion-independent, transfusion therapy is still needed by these patients in certain clinical situations. Examples of such scenarios include: pregnancy (due to exaggerated anaemia), surgery or any setting with anticipated acute blood loss, infections, and failure to thrive during childhood.¹

---

**Figure 2: Treatment modalities available for treating non-transfusion-dependent thalassaemia patients.**

HbF: fetal haemoglobin.
In fact, transfusions have been observed to greatly improve the prognosis of certain complications of NTDT such as leg ulcers, thrombotic events, silent brain infarcts, and pulmonary hypertension.\textsuperscript{2,20,24,57,58} Blood transfusions can also suppress extramedullary haematopoeisis and its sequelae, particularly paraspinal pseudotumours.\textsuperscript{59} Yet, because iron overload is a major concern in NTDT, blood transfusions should not be given to patients in this disease group unless absolutely indicated (Figure 3).

**Surgical**

The spleen is responsible for the sequestration of one-third of the platelets that are produced by the bone marrow and the removal of pathological red blood cells. In NTDT patients, splenectomy might increase haemoglobin levels by 1–2 g/dL and as such decrease the need for blood transfusions.\textsuperscript{33,38} However, splenectomy is associated with an increased incidence of venous thromboembolic events, silent cerebral infarcts, pulmonary hypertension, and leg ulcers.\textsuperscript{60} On that account, splenectomy in NTDT patients is reserved for the following cases:\textsuperscript{2,17}

- Worsening of anaemia, thrombocytopenia causing haemorrhages, and/or leukopenia causing recurrent bacterial infections, all as a result of hypersplenism
- Splenomegaly causing early satiety due to gastric displacement, or a palpable, left upper quadrant abdominal mass that might be painful and can eventually rupture
- Poor growth and failure to thrive in cases where transfusions and iron chelating drugs are not possible or unavailable

**QUALITY OF LIFE**

When managing a thalassaemic patient, applying a patient-centred approach is key to successful outcomes. Equally important to controlling symptoms and preventing complications is assessing the patient’s health-related quality of life. It is therefore recommended to closely follow
all patients, both medically and psychologically, while attempting to involve them as much as possible in treatment decision making and providing them with support whenever needed.²

CONCLUSIONS AND FUTURE PROSPECTS

The prevalence of NTDTs has recently started to take on a global distribution³³ and thus calls for serious action. Early diagnosis, including prenatal diagnosis and screening, neonatal screening, and treatment of complications in an approach tailored to the individual patient typify the mainstay of managing NTDT patients. Needless to say, preventive measures are central to the management protocol, where the importance of public awareness and premarital counselling and screening cannot be overstated.⁶¹ Also pivotal is the role of reproductive technologies in preventing births of affected children, in addition to the role of education programmes in decreasing marriages between carriers.⁶¹ The strategy combining the aforementioned modalities is often described as the most effective in rapidly reducing the counts of affected births, where its use in Cyprus has led to the eradication of thalassaemia, and its implementation in Lebanon at the Chronic Care Center (the only specialised centre in Lebanon for thalassaemia treatment and prevention) has contributed to a decrease in thalassaemia births in the country of >75%.⁶¹ On a separate note, several novel therapeutics have recently stemmed from a better understanding of the pathophysiological mechanisms underlying NTDT, and many of these strategies are currently being developed in clinical trial programmes. Examples of agents that are currently under investigation are: a recombinant fusion protein comprised of modified activin receptor type IIIB (ActRIIB; a member of the transforming growth factor beta superfamily) and human immunoglobulin G1 Fc, Janus kinase 2 (JAK2) inhibitors, hepcidin mimetics, and apotransferrin therapy.⁵,³³ Other molecules, including BCL11A, MYB, and KLF1 which have been newly identified by human genetic studies, might provide promising therapeutic targets by inducing fetal haemoglobin.³³ Gene therapy is another promising treatment modality that stems from the concept of ‘fixing’ one’s bone marrow cells by transferring the normal α or γ gene into haematopoietic stem cells to permanently produce normal red blood cells.⁵⁰ Interestingly, growing evidence over the years has recognised the discerning aptitude of a holistic approach ranging all the way from identification of at-risk populations and implementation of screening and prenatal diagnosis programmes, to comprehensive patient education and patient management strategies targeted at the impairments that adversely impact quality of life, such as anaemia and iron burden.⁶²⁻⁶⁴

REFERENCES

18. Taher A et al. Overview on practices in thalassemia intermedia management.


