Morbidities in Non-Transfusion-Dependent Thalassemias (NTDT)

Thalassemia Intermedia: is disease morbidity as we know it today less severe than Thalassemia Major?

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Agenda

- Non-transfusion-dependent thalassemia (NTDT)
- Morbidity in NTDT
  - Clinical complications profile
  - Ineffective erythropoiesis and anemia
  - Iron overload and target organ damage
  - Hypercoagulability and vascular disease
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NTDT: a designation based on transfusion requirement

Non transfusion dependent thalassaemia (NTDT)
- β-thalassaemia intermedia
- Mild/moderate HbE/β-thalassaemia
- HbH disease (α-thalassaemia)
- HbS β-thalassaemia
- HbC thalassaemia

Transfusions not required
- α-thalassaemia trait
- β-thalassaemia minor

Transfusions seldom required

Occasional transfusions required (e.g. surgery, pregnancy, infection)

Intermittent transfusions required (e.g. poor growth and development, specific morbidities)

Regular, lifelong transfusions required for survival

Transfusion dependent thalassaemia (TDT)
- β-thalassaemia major
- Severe HbE/β-thalassaemia
- Hb Barts hydrops (α-thalassaemia major)

NTDT patients do not require regular transfusions, although they may require occasional transfusions for growth failure, pregnancy, infections, and other specific situations\(^1-4\)

3. Vichinsky E. Hematology Am Soc Hematol Educ Program. 2007;79-83. 4
5. Figure adapted from Musallam KM, et al. Haematologica. 2013;98:833-44.

HbE, haemoglobin E; HbH, haemoglobin H.
The prevalence of NTDT is increasing worldwide due to migration

Prevalence of Hb H disease in Europe and North America increasing due to migration

β thalassemia intermedia – most common in Africa, Mediterranean, India and East Europe

Hb H – most common in Southeast Asia, Middle East and Mediterranean
Approx. 9500 annual births

Hb E/β thalassemia – most common in East India, Bangladesh and Southeast Asia
Approx. 19,000 annual births

The increased migration flow expands the reach of these diseases

1Weatherall DJ. Blood Rev 2012;26 Suppl 1:S3–S6;
2Available from: http://emedicine.medscape.com/article/959122-overview#a0156;
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  - Hypercoagulability and vascular disease
How it all started: realizing morbidity is highly prevalent and different from TDT in our clinics

<table>
<thead>
<tr>
<th>Complication (% of patients affected)</th>
<th>β-TI Lebanon (n = 37)</th>
<th>β-TI Italy (n = 63)</th>
<th>β-TM Lebanon (n = 40)</th>
<th>β-TM Italy (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomy</td>
<td>90</td>
<td>67</td>
<td>95</td>
<td>83</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>85</td>
<td>68</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Gallstones</td>
<td>55</td>
<td>63</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Extramedullary haemopoiesis</td>
<td>20</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>20</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>28</td>
<td>22</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiopathy(^a)</td>
<td>3</td>
<td>5</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>PHT(^b)</td>
<td>50</td>
<td>17</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Abnormal liver enzymes</td>
<td>20</td>
<td>22</td>
<td>55</td>
<td>68</td>
</tr>
<tr>
<td>HCV infection</td>
<td>7</td>
<td>33</td>
<td>7</td>
<td>98</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>5</td>
<td>3</td>
<td>80</td>
<td>93</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
<td>2</td>
<td>12.5</td>
<td>10</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3</td>
<td>2</td>
<td>15</td>
<td>11</td>
</tr>
</tbody>
</table>

\(^a\) Fractional shortening < 35%.
\(^b\) Defined as pulmonary artery systolic pressure > 30 mmHg; a well-enveloped tricuspid regurgitant jet velocity could be detected in only 20 patients, so frequency was assessed in these patients only.
### β-Thalassemia Major
(Regularly transfused)

- Facies
- Bone deformity (Hair on end)
- Hypothyroidism
- Hypoparathyroidism
- Cardiac siderosis
- Left-sided heart failure
- Hepatic failure
- Viral hepatitis
- Diabetes mellitus
- Hypogonadism
- Osteoporosis

### Non-Transfusion-Dependent Thalassemias (NTDT)

- Silent cerebral ischemia
- Pulmonary hypertension
- Right-sided heart failure
- Extramedullary hematopoietic pseudotumors
- Hepatic fibrosis, cirrhosis and cancer
- Gall stones
- Splenomegaly
- Osteoporosis
- Venous thrombosis
- Leg ulcers

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Observations were similar in reported literature

Better understanding of the morbidity profile and associated risk factors was thus warranted and motivated a large research program to revisit morbidity in NTDT patients.
The OPTIMAL CARE study
Overview on Practices in β-Thalassaemia Intermedia Management
Aiming for Lowering Complication rates Across a Region of Endemicity:

- Cross-sectional study of 584 patients with β-TI from 6 comprehensive care centres in the Middle East and Italy

n = 127
A.T. Taher
K.M. Musallam

n = 200
M. Karimi

n = 12
S. Daar

n = 153
M.D. Cappellini

n = 51
A. El-Beshlawy

n = 41
K. Belhoul
M. Saned

β-TI, β-thalassaemia intermedia.

High morbidity rates were confirmed

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequency</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 18</td>
<td>172 (29.5)</td>
<td></td>
</tr>
<tr>
<td>18–35</td>
<td>288 (49.3)</td>
<td></td>
</tr>
<tr>
<td>&gt; 35</td>
<td>124 (21.2)</td>
<td></td>
</tr>
<tr>
<td>Male:female</td>
<td>291 (49.8) : 293 (50.2)</td>
<td></td>
</tr>
<tr>
<td>Splenectomized</td>
<td>325 (55.7)</td>
<td></td>
</tr>
<tr>
<td>Serum ferritin (µg/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1,000</td>
<td>376 (64.4)</td>
<td></td>
</tr>
<tr>
<td>1,000–2,500</td>
<td>179 (30.6)</td>
<td></td>
</tr>
<tr>
<td>&gt; 2,500</td>
<td>29 (5)</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>134 (22.9)</td>
<td></td>
</tr>
<tr>
<td>EMH</td>
<td>124 (21.2)</td>
<td></td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>101 (17.3)</td>
<td></td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>100 (17.1)</td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td>82 (14)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>64 (11)</td>
<td></td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>57 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>46 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>33 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>25 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (1.7)</td>
<td></td>
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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Frequency</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Hydroxyurea</td>
<td>202 (34.6)</td>
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<tr>
<td>Transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>139 (23.8)</td>
<td></td>
</tr>
<tr>
<td>Occasional</td>
<td>143 (24.5)</td>
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<tr>
<td>Regular</td>
<td>302 (51.7)</td>
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<tr>
<td>Iron chelation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>248 (42.5)</td>
<td></td>
</tr>
<tr>
<td>Deferoxamine</td>
<td>300 (51.4)</td>
<td></td>
</tr>
<tr>
<td>Deferiprone</td>
<td>12 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Deferiprone + deferoxamine</td>
<td>3 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Deferasirox</td>
<td>21 (3.6)</td>
<td></td>
</tr>
</tbody>
</table>
Morbidities seemed to increase with advancing age

ALF, abnormal liver function; DM, diabetes mellitus; HF, heart failure.

The pathophysiology and risk factors were predicted ... but not yet evaluated.
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- Morbidity in NTDT
  - Clinical complications profile
  - Ineffective erythropoiesis and anemia
  - Iron overload and target organ damage
  - Hypercoagulability and vascular disease
As the primary source of disease process, the question was how can ineffective erythropoiesis and anemia lead to such a diverse complication profile?
Ineffective erythropoiesis in untreated patients with β-thalassemia intermedia
Ineffective erythropoiesis leads to iron overload in NTDT

Ineffective erythropoiesis
Chronic anemia/hypoxia

↑ Erythropoietin

↓ Hepcidin

↓ Ferroportin
Intestinal iron absorption

↑ Release of recycled iron from reticuloendothelial system

Transfusions

Minor role

Iron overload

Chronic anemia is also independently associated with clinical morbidity and iron overload in NTDT

A hemoglobin of <7 g/dL was the level below which all patients developed a morbidity while a hemoglobin of >10 g/dL was the level after which none of the patients had a morbidity (area under the curve = 0.84, 95% CI: 0.70 to 0.97, \( p < 0.001 \))

Pearson's \( r = -0.5951, \ p < 0.001 \)

Extramedullary hematopoietic pseudotumors in NTDT as a result of ineffective erythropoiesis and anemia/hypoxia

- Thoracic and lumbar regions are most commonly involved
- Symptoms develop as a result of pressure on surrounding structures
- Spinal cord compression and possible irreversible neurological damage is most significant and debilitating

Leg ulcers in NTDT can develop in the context of anemia and tissue hypoxia

Leg ulcers are more common in older than in younger patients with β-TI

The skin at the extremities of elderly β-TI patients can be thin due to reduced tissue oxygenation; this makes the subcutaneous tissue fragile and increases the risk of lesions

Ulcers are very painful and difficult to cure

Risk factors: severe anaemia, ineffective erythropoiesis, splenectomy, and hypercoagulability levels

A role for local IOL is suggested; IOL may play a role in the pathophysiology of leg ulcers by causing oxidative stress and not just by local accumulation

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Since it was apparent that NTDT patients develop iron overload in the absence of transfusions, the question was should we be concerned with this iron overload?
Iron overload in NTDT

- **Cumulative process**
  - Positive correlations between iron overload indices and advancing age\(^1\)\(^-\)\(^5\)
- **Slower than transfusional siderosis**
  - 3-4 mg/day or as much as 1,000 mg/year\(^6\)
  - Annual increase in liver iron concentration of 0.38 ± 0.49 mg Fe/g dry\(^7\)

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SF levels increased over 11 years in 52 non-chelated β-TI patients: The ORIENT study

Mean serum ferritin level and 95% CI

Iron overload and the heart

No evidence of cardiac siderosis even in NTDT patients with considerable iron overload\textsuperscript{1-4}

HCC is one of the most clinically severe complications of NTDT & may be related to iron overload

Several case reports and case series suggest an association between iron overload and HCC in hepatitis C-negative patients with NTDT

Possible reasons for increased risk of HCC in NTDT

- Iron overload is undiagnosed (serum ferritin underestimates iron burden compared with TDT)
- Chelation is started late or not at all
- NTDT patients survive longer than TDT, often an older population
- Hepatocellular > macrophage distribution

HCC found in non-viral, non-cirrhotic livers, highlighting the potential severity of iron overload and its complications

- Case reports and case series in the literature reviewed for consistency between patient characteristics
- HCC observed in patients with non-viral (hepatitis), non-cirrhotic livers
  - Of 36 cases, 22 were β TI patients, of whom six were negative for hepatitis B or C
- Survey for HCC using an abdominal ultrasound every 6 months is recommended in at-risk patients

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age*</th>
<th>Survival</th>
<th>HCV Ab</th>
<th>HCV RNA</th>
<th>HBV Ab</th>
<th>HBs Ag</th>
<th>AFP (kU/L)</th>
<th>Serum ferritin (ng/mL)</th>
<th>Serum ferritin peak (ng/mL)</th>
<th>LIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>48</td>
<td>Alive at 26 months</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2851</td>
<td>1520</td>
<td>5250</td>
<td>NA</td>
</tr>
<tr>
<td>F</td>
<td>61</td>
<td>5 months</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>132</td>
<td>369</td>
<td>6000</td>
<td>NA</td>
</tr>
<tr>
<td>F</td>
<td>59</td>
<td>25 months</td>
<td>+</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>990</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>M</td>
<td>73</td>
<td>7 months</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>574</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>M</td>
<td>54</td>
<td>1 months</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>17.8</td>
<td>1291</td>
<td>2490</td>
<td>12.3</td>
</tr>
<tr>
<td>M</td>
<td>51</td>
<td>4 years</td>
<td>–</td>
<td>–</td>
<td>Vaccinated</td>
<td>–</td>
<td>3.8</td>
<td>5602</td>
<td>7138</td>
<td>23.9</td>
</tr>
</tbody>
</table>

HCC is a serious yet often overlooked complication in NTDT with appropriate screening, early detection and adequate iron chelation, complications can be minimized

*At diagnosis
Ab, antibody; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen

Iron overload and liver fibrosis

Transient elastography values corresponding to fibrosis stages are: ≤7.9 kPa for S <3; >7.9 to 10.3 for S 3; >10.3 to 12.0 for S 4; and >12.0 for S 5.

Patients with iron overload had higher fibrosis values on Fibroscan

Iron overload and other morbidities

On multivariate analysis, a 1 mg Fe/g dw increase in LIC was significantly associated with higher odds of **thrombosis, pulmonary hypertension, hypothyroidism, osteoporosis, and hypogonadism**

*Adjusted for age, gender, splenectomy status, transfusion history, total hemoglobin level, fetal hemoglobin level, platelet count, NRBC count, and serum ferritin level*

Renal dysfunction in thalassemia is generally caused by persistent hypoxia, anemia, and severe IOL

**Anemia**
- Glomerular dysfunction
  - ↓ vascular resistance results in
  - ↓ GFR

**Hypoxia**
- Tubulointerstitial dysfunction
  - epithelial–mesenchymal transdifferentiation
  - accumulation of extracellular matrix
  - activation of fibroblasts
  - ↓ diffusion capacity of oxygen

**Iron overload**
- Tubulointerstitial dysfunction
  - direct iron cytotoxicity on tubules and
glomerular permeability causes enzymuria +
proteinuria
  - moderate tubular atrophy and interstitial fibrosis

**Iron chelation**
- Tubular dysfunction
  - vacuolization of proximal tubular epithelium
  - apoptosis of tubule cell
  - ↓ tubular absorption of solutes
- Glomerular dysfunction
  - reversible haemodynamic changes

**Glomerular dysfunction**
- mild to moderate glomerulosclerosis
  - ↓ GFR

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GFR, glomerular filtration rate.

Renal dysfunction in β-TI is associated with iron overload

- 48% had evidence of glomerular hyperfiltration
- 14% patients had proteinuria* → patients had elevated LIC>7 mg Fe/g dw, NTBI and nucleated RBC counts

A considerable proportion of patients showed evidence of abnormally elevated eGFR, with a declining trend towards advancing age

Occurrence of proteinuria associated with anemia, hemolysis and iron toxicity

*UPr/UCr ratio >500 mg/g

Long-term follow-up of NTDT patients is crucial to identify TI patients at risk of end-stage renal disease

- 127 TI patients were observed for 10 years
- 6 (4.7%) developed ESRD that required regular haemodialysis
  - 4 showed no abnormality in urine sediment or proteinuria
  - 2 showed glomerular-range proteinuria
    - 1 reached nephrotic range (biopsy showed FSGS)

ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis.

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  - Ineffective erythropoiesis and anemia
  - Iron overload and target organ damage
  - Hypercoagulability and vascular disease
Surely, iron overload is not the only risk factor for morbidity, so the question was what other key players are involved?
Hypercoagulability and vascular disease in NTDT

- Transfusion:
  - ↓ Antithrombin III
  - ↓ Protein C
  - ↓ Protein S
- Splenectomy:
  - ↑ Endothelial injury
    - Expression of adhesion molecules and tissue factor
    - ↑ Circulating microparticles
- Iron overload:
  - ↑ Platelet abnormalities
    - Thrombocytosis
    - Chronic activation
    - ↑ Adhesion and aggregation
- Pathologic RBCs:
  - ↑ Thrombin generation (phosphatidyl serine exposure)
  - ↑ Rigidity, deformability, and aggregation
- Endothelial injury:
  - ↑ Circulating microparticles
- Platelet abnormalities:
  - ↑ Adhesion and aggregation
- Endocrine & hepatic dysfunction
- ↑ Atherosclerosis

Hemoglobin

Denaturation

Excess α-chains

Hemichromes

Inclusion bodies

Band 3 clustering

Spectrin & Band 3 abnormalities

PS exposure

Degradation

Fe²⁺

Oxidation

ROS

PS

FVα, FXa, FII

↓ Protein C & S

↓ RBC adhesion & aggregation

↑ Platelet activation & adhesion

↑ Platelet activation

↑ WBC activation

Thrombin

Thrombus formation

Endothelial damage/activation

Thromboembolic events in a large cohort of β-TI patients

- Patients (N = 8,860)
  - 6,670 with β-TM
  - 2,190 with β-TI
- 146 (1.65%) thrombotic events
  - 61 (0.9%) with β-TM
  - 85 (3.9%) with β-TI
- Risk factors for developing thrombosis in β-TI were
  - age (> 20 years)
  - previous thromboembolic event
  - family history
  - splenectomy

DVT = deep vein thrombosis
PVT = portal vein thrombosis; STP = superficial thrombophlebitis

OPTIMAL CARE study: multivariate analysis on risk factors for thrombosis in splenectomised patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRBC count ≥ 300 x 10⁶/L</td>
<td>Group III</td>
<td>1.00</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group II</td>
<td>5.35</td>
<td>2.31–12.35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Group I</td>
<td>11.11</td>
<td>3.85–32.26</td>
<td></td>
</tr>
<tr>
<td>Platelet count ≥ 500 x 10⁹/L</td>
<td>Group III</td>
<td>1.00</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group II</td>
<td>8.70</td>
<td>3.14–23.81</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Group I</td>
<td>76.92</td>
<td>22.22–250.00</td>
<td></td>
</tr>
<tr>
<td>PHT</td>
<td>Group II</td>
<td>4.00</td>
<td>0.99–16.13</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>Group I</td>
<td>7.30</td>
<td>1.60–33.33</td>
<td></td>
</tr>
<tr>
<td>Transfusion naivety</td>
<td>Group III</td>
<td>1.00</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group II</td>
<td>1.67</td>
<td>0.82–3.38</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Group I</td>
<td>3.64</td>
<td>1.82–7.30</td>
<td></td>
</tr>
</tbody>
</table>

Group I patients had significantly higher NRBC, platelets, and PHT occurrence, and were mostly non-transfused.

NRBC = nucleated red blood cell; PHT = pulmonary hypertension; OR = adjusted odds ratio; CI = confidence interval.

## Silent cerebral infarction in splenectomized patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>MRI technique</th>
<th>Definition of infarction</th>
<th>Prevalence of SCI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manfre et al. 1999</td>
<td>16</td>
<td>Mean: 29</td>
<td>0.5 Tesla, T2- spin-echo weighted imaging</td>
<td>Abnormally high signal intensity on long TR-weighted images, Two blinded neuroradiologists</td>
<td>37.5% (18.4-61.7)</td>
</tr>
<tr>
<td>Taher et al. 2010</td>
<td>30</td>
<td>Mean: 32.1</td>
<td>3.0 Tesla, T1-, T2-gradient-echo-, FLAIR-, diffusion-weighted imaging</td>
<td>Abnormally high signal intensity on the T2- and FLAIR-weighted images, Two blinded neuroradiologists</td>
<td>60.0% (42.2-75.5)</td>
</tr>
<tr>
<td>Karimi et al. 2010</td>
<td>30</td>
<td>Mean: 24.3</td>
<td>1.5 Tesla, T1-, T2-, FLAIR-weighted imaging</td>
<td>Abnormally high signal intensity on the T2- and FLAIR- weighted images, One neuroradiologist</td>
<td>26.7% (14.2-44.6)</td>
</tr>
<tr>
<td>Teli et. al 2012</td>
<td>24</td>
<td>Mean: 12</td>
<td>N/A</td>
<td>N/A, 0%</td>
<td></td>
</tr>
</tbody>
</table>

*a* Other diagnoses were ruled out based on the radiological appearance of lesions (e.g. viral encephalopathy or multiple sclerosis) or absence of associated risk factors and clinical symptoms (e.g. vasculitis or Binswanger’s disease).

FLAIR, fluid attenuation inversion recovery; N/A, data not available; CI, confidence interval.

Risk factors for silent cerebral infarction

Increasing age and transfusion naivety are associated with a higher incidence and multiplicity of white matter lesions.

Other cerebrovascular complications in splenectomized β-TI patients

- Large vessel stenosis on MRA\(^1\)
  - Association with anemia and high NTBI

- Decreased neuronal function on PET-CT\(^2\)
  - Association with elevated LIC

## Risk factors for PHT: OPTIMAL CARE

<table>
<thead>
<tr>
<th>Parameters</th>
<th>( \beta-TI ) patients (N = 64)</th>
<th>( \beta-TI ) patients (N = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PHT+*</td>
<td>PHT−</td>
</tr>
<tr>
<td>Splenectomized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>84.4</td>
<td>46.9</td>
</tr>
<tr>
<td>AOR (95% CI)</td>
<td>4.9 (1.9–8.5)</td>
<td></td>
</tr>
<tr>
<td>History of thromboembolic events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>40.6</td>
<td>7.8</td>
</tr>
<tr>
<td>AOR (95% CI)</td>
<td>3.69 (2.38–7.05)</td>
<td></td>
</tr>
<tr>
<td>Nucleated RBC count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD; x 10^6/L)</td>
<td>354.2 (199.2)</td>
<td>214.7 (94.5)</td>
</tr>
<tr>
<td>AOR (95% CI)</td>
<td>2.59 (1.69–6.05)</td>
<td></td>
</tr>
<tr>
<td>Transfusion naivety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>56.2</td>
<td>78.1</td>
</tr>
<tr>
<td>AOR (95% CI)</td>
<td>3.5 (2.1–6.25)</td>
<td></td>
</tr>
<tr>
<td>Iron chelation naivety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>37.5</td>
<td>62.5</td>
</tr>
<tr>
<td>AOR (95% CI)</td>
<td>2.3 (1.2–4.25)</td>
<td></td>
</tr>
<tr>
<td>Hydroxyurea naivety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>17.2</td>
<td>34.4</td>
</tr>
<tr>
<td>AOR (95% CI)</td>
<td>2.6 (1.1–5.25)</td>
<td></td>
</tr>
</tbody>
</table>

* \( p < 0.001 \) for all parameters for patients with PHT versus those without PHT

AOR = adjusted odds ratio

Risk of Pulmonary Hypertension in NTDT increases with high LIC, advancing age, and splenectomy

PHT (defined as PASP ≥ 30 mmHg) present in 38.5%

Significantly correlated with LIC
Not correlated with age, Hb level, and SF level

PHT prevalence in thalassaemia was 2.1%
(TI 4.8%, TM 1.1%)

PASP, pulmonary artery systolic pressure; TCG, tricuspid gradient.
With all this morbidity it was not surprising that β-TI patients had poor HR-QoL

*P < 0.05

Takeaways

• There is a high prevalence of morbidities in NTDT patients and their prevalence increases with age, starting at the age of 10 years.

• Morbidities in NTDT stem from the interaction of multiple pathophysiological factors: ineffective erythropoiesis, iron overload (IOL), and hypercoagulability.

• Ineffective erythropoiesis and hemolysis are also associated with a hypercoagulable state, ultimately leading to a high incidence of thromboembolic and cerebrovascular events, as well as pulmonary hypertension.

• Ineffective erythropoiesis is associated with low hepcidin levels, which subsequently lead to IOL.
Takeaways

• IOL in NTDT patients is a cumulative process that can lead to several iron-related morbidities in the liver (liver fibrosis), endocrine glands (endocrinopathies), and vascular system (vascular disease).

• There exists an association between IOL and hepatocellular carcinoma (HCC) in hepatitis C-negative patients with NTDT, suggesting that HCC is a newly emerging adverse complication as a consequence of the prolonged survival of thalassemia patients.

• Renal dysfunction in NTDT has also been described and is caused by persistent hypoxia, anemia, and severe IOL.