Thalassaemia Case Scenarios

Dr Emma Drasar
Haematology Consultant
The Whittington Hospital
With transfusion and chelation therapy, thalassemia patients can be expected to have a normal life, shifting the focus to managing the disease complications.

**Survival probability**

- Birth cohort:
  - 1980–1984
  - 1975–1979
  - 1965–1969
  - 1960–1964

- *p < 0.00005*

**β-thalassemia major (regularly transfused, TDT)**
- 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 hemopoietic pseudotumors
- Hematopoesis, cirrhosis, and cancer
- Gallstones
- Splenomegaly
- Osteoporosis
- Venous thrombosis
- Leg ulcers

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IOL, iron overload; TDT, transfusion-dependent thalassemia.

Guidance for the clinician


Complication 1

- 26 year old man
- Attends for routine cross match
- Mentions to Thalassaemia nurse that he was found on the floor last night by flat mates
- Has no memory of what happened.
- What would you do?
Complication 1

- Now feels fine
- Does say has had sensation of “skipped beats” for last month.
- Poorly compliant with chelation

Next investigations?
Complication 1

- ECG
- 48 hour tape
- Admit and IV desferral with view to introducing deferiprone ASAP

Mildly dilated LV with impairment, EF 52%. Severe liver (0.86ms) and myocardial (2.1ms) iron loading. Both on 2-point curve. “We see one such severe cardiac iron overload every 3-5 years”.

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London
## Complication 1

### Why does iron overload in the heart matter?

### Guidelines for Iron Assessment

<table>
<thead>
<tr>
<th>Myocardial loading</th>
<th>Myocardial T2*(ms)</th>
<th>Hepatic loading</th>
<th>Hepatic T2* (ms)</th>
<th>Dry weight (Anderson)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>&gt;20ms</td>
<td>None</td>
<td>&gt;6.3ms</td>
<td>&lt;2mg/g</td>
</tr>
<tr>
<td>Mild</td>
<td>&gt;14-20ms</td>
<td>Mild</td>
<td>&gt;2.7- 6.3ms</td>
<td>2-&gt;5mg/g</td>
</tr>
<tr>
<td>Moderate</td>
<td>10-14ms</td>
<td>Moderate</td>
<td>1.4-2.7ms</td>
<td>5-10mg/g</td>
</tr>
<tr>
<td>Severe*</td>
<td>&lt;10ms</td>
<td>Severe</td>
<td>&lt;1.4ms</td>
<td>&gt;10mg/g</td>
</tr>
</tbody>
</table>

*Severe indicates a higher level of iron overload than the other categories.*
LVEF, arrhythmia and cardiac failure associated with cardiac IOL

Myocardial T2* values < 20 ms are associated with a progressive and significant decline in LVEF

Significant reduction in cardiac mortality in the past two decades with new chelators and diagnostics

- The age at the time of death from cardiac mortality increased in parallel with the decrease of cardiac mortality
- The prognosis of β-TM patients significantly improved with
  - non-invasive methods to measure organ iron
  - new chelators
  - increased blood safety measures

Complication 2

- 45 year old beta thal major patient presents to A&E with nausea, confusion and polyuria and polydypsia.
  - How would you investigate them?
  - What is the underlying cause?
Complication 2

- Treat as you would any other patient with HHS but think about cardiac function
- Screening for DM and control – annual OGTTs and regular fructosamines
- Role of joint clinics and MDT to improve compliance
- Diabetes nurse reviewing patient while they have their transfusion
- Phone clinics
Endocrinopathies increase with age in TDT patients

## Older thalassaemia major patients

<table>
<thead>
<tr>
<th>Endocrinopathy (N= number with status of endocrinopathy known)</th>
<th>Prevalence (%) of endocrinopathy within Age Group</th>
<th>Overall Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus (DM) (N=88)</td>
<td>&lt; 30 years 24 (25%) 15/33 (46%) 15/31 (48%) 36/88 (41%)</td>
<td></td>
</tr>
<tr>
<td>Impaired fasting glycaemia (IFG)/Impaired glucose tolerance (IGT) (N=88)</td>
<td>7/24 (29%) 8/33 (24%) 2/31 (7%) 17/88 (19%)</td>
<td></td>
</tr>
<tr>
<td>Hypogonadism (HG) (N=94)</td>
<td>14/24 (58%) 25/36 (69%) 25/34 (74%) 64/94 (68%)</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism (HT) (N=92)</td>
<td>2/24 (8%) 7/35 (20%) 4/33 (12%) 13/92 (14%)</td>
<td></td>
</tr>
<tr>
<td>Hypoparathyroidism (HP) (N=82)</td>
<td>0/23 (0%) 2/31 (6%) 2/28 (7%) 4/82 (5%)</td>
<td></td>
</tr>
<tr>
<td>≥ 1 endocrinopathy* (N=75)</td>
<td>14/22 (63%) 20/28 (71%) 19/25 (76%) 54/75 (71%)</td>
<td></td>
</tr>
<tr>
<td>≥ 2 endocrinopathy* (N=75)</td>
<td>7/22 (32%) 15/28 (54%) 12/25 (48%) 34/75 (45%)</td>
<td></td>
</tr>
<tr>
<td>≥ 3 endocrinopathy* (N=75)</td>
<td>0/22 5/28 (18%) 4/25 (16%) 9/75 (12%)</td>
<td></td>
</tr>
</tbody>
</table>

Ang et al 2013 EJH
Complication 3

• What is this and what could have led to its development in a patient with thalassaemia?

• What can we do to prevent it from happening to future patients?
Liver complications are becoming more prominent.

\[ n = 4,506, \text{ of whom } 2,485 (52.3\%) \text{ with TM} \]

HCC is a major cause of death in HH and NTDT

- HCC generally occurs on a cirrhotic substrate
  - yearly incidence rate approximately 3% in HH; no data for NTDT
- HCC is the main cause of morbidity and mortality in adult HH and is increasing in thalassaemia (particularly NTDT)
  - of 36 thalassaemic patients with HCC, 22 (61%) had β-TI, including 6 who were HCV negative (probably almost all had liver cirrhosis)
- Reasons for increased risk
  - IOL remains unnoticed and untreated
    - patients are asymptomatic
    - iron burden was underestimated in β-TI patients
  - patients with an adult form of HH and β-TI patients survive longer
    - higher risk of cirrhosis and more time for HCC development

HCC, hepatocellular carcinoma; T I, thalassaemia intermedia.


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Recommendations?

• All patients who have EVER had a liver biopsy with evidence of cirrhosis or fibrosis should be on surveillance for HCC
  – Six monthly ultrasound scans
  – Endoscopy annually

• Any patients with severe iron overload at any time in the past should be tested to identify fibrosis/cirrhosis (fibroscan or other method) and then enter surveillance
Complication 4

• 42 year old thalassaemia major patient presents with high temperature, unwell with loin to groin pain.

• What could be causing this?

• Renal function has been deteriorating over past 5 years. What could be contributing to this situation?
Complication 4

- Renal complications increasingly common in thalassaemia:
  - Renal tubulopathy
  - Renal stones
  - Renal cell carcinoma
Nephrolithiasis

Renal stones

- Probability of forming a stone
  - Asia 1–5%
  - Europe 5–9%
  - North America 13%
  - Saudi Arabia 20%
- 1–2% occurrence in children

- Types
  - Ca$^{2+}$ oxalate/phosphate 50–70%
  - uric acid 10–23%
  - struvite 5–10%
  - cysteine 1–2%

Idiopathic hypercalciuria

- Hyperparathyroidism
- Sarcoidosis
- Vitamin D intake
- Distal renal tubular acidosis
- Lithium
- Hypercalcaemic syndromes
  - tumour, etc.
- Hereditary

Mechanisms of renal disease in thalassaemia

Chronic anaemia or hypoxia
- Vascular resistance
- Renal plasma flow
- GFR
- Endothelial and epithelial damage
- Transudation of macromolecules
- Mesangial dysfunction
- GFR

Iron overload
- Tubular cell damage
- Epithelia–mesenchymal transdifferentiation
- Tubulointerstitial injury
- Glomerular sclerosis
- GFR

Iron chelation
- Relative iron depletion
- Abnormal mitochondrial function and arachidonic acid cascade
- Tubuloglomerular feedback and haemodynamic change
- GFR

Tubular cells
- Oxidative stress
- Lipid peroxidation
- Cellular damage

Nephrotoxicity

Conclusion

• New complications developing as well as the preexisting ones
• Thalassaemia patients are reaping the benefits of longer survival but also a whole new lot of complications
• Long term impact of iron overload is resulting in new problems