IMPROVING DIAGNOSIS, REDUCING MISDIAGNOSIS – THE CASE OF THALASSAEMIA

Dr Androulla Eleftheriou
Executive Director, Thalassaemia International Federation
President, Cyprus Alliance for Rare Disorders
Member of the Board of Directors of the International Alliance for Patient Organizations (IAPO)

Thursday 23 May 2019
Universal Health Coverage: Including Rare Diseases to leave no-one behind
Informal Side Event, 72nd World Health Assembly
Thalassaemia International Federation (TIF)

Established in **1986** as a
- Non-profit
- Non-governmental
- Patient/parent-driven

**5 Founding Members** from National Patient Associations of Cyprus, Italy, Greece, USA, UK – the first members

**6 Medical Advisors** forming the Scientific Advisory Panel

Supported by the World Health Organisation

**Mission:** Development and implementation of national disease – specific control programmes within national healthcare systems based on universal coverage

**Vision:** Equal and timely access to quality health, social and other care for all patients with thalassaemia globally, in a truly patient-centred healthcare setting

**Values:**
- Patient-centredness
- Strong patients’ voice
- Health and social equity
- Accountability
- Transparency
- Ethos
- Independence

**1996:** TO ACHIEVE ITS MISSION TIF IS FIGHTING FOR:
(i) POLITICAL RECOGNITION OF THE DISEASE BURDEN, NATIONAL/INTERNATIONAL LEVEL
(ii) POLITICAL COMMITMENT TO BUILD AND SUSTAIN NATIONAL CONTROL PROGRAMMES

**2003:** TIF NEEDS TO ACHIEVE:
(1) POLITICAL COMMITMENT AT THE NATIONAL, REGIONAL, INTERNATIONAL LEVEL
   - INCREASE OF GOVERNMENT HEALTH EXPENDITURE
   - PROVISION OF FULL COVERAGE/REIMBURSEMENT FOR CHRONIC DISEASES
(2) NEED TO PRIORITISE Hb DISORDERS ON WHO’S PROGRAMMES:
   - NON-COMMUNICABLE DISEASES (NCD) (WHA61.14)
   - BIRTH DEFECTS (WHA61.17)
(3) NEED TO MONITOR IMPLEMENTATION OF WHO RESOLUTIONS:
   - SPECIFIC: WHA61.18 (THALASSAEMIA); WHA61.19 (SICKLE CELL ANAEMIA)
   - NON-SPECIFIC: WHA63.12 (AVAILABILITY, SAFETY, AND QUALITY OF BLOOD PRODUCTS); WHA63.18 (VIRAL HEPATITIS); WHA63.19 (COUNTERFEIT/SPURIOUS MEDICINES)
Thalassaemia International Federation (TIF)

227 National Patient Associations in 61 countries
216 Medical Advisors
63 Patient volunteers

Wide Network of Collaborators:
- 8 Medical, Scientific & Academic bodies, associations & societies
- 16 Patient NGOs at European & International levels
- 36 Industry organisations / companies

Mission: Development and implementation of national disease-specific control programmes within national healthcare systems

Vision: Equal and timely access to quality health, social and other care for all patients with thalassaemia globally, in a truly patient-centred healthcare setting

Values:
- Patient-centricity
- Strong patients' voice
- Health and social equity
- Accountability
- Independence
- Transparency
- Ethos

In 2019

Working in official relations with the World Health Organization (WHO) since 1996

In special consultative status with the United Nations Economic and Social Council (ECOSOC) since 2017

Official Partners of the European Commission in the field of Health since 2018

TIF Members Global Representation
Thalassaemia is no longer a fatal disease of childhood, but this is not the case globally.

Medical /public health impact

Pathophysiology of β-thalassemia

Source: New England Journal of Medicine
Consequences of Un-diagnosis / Misdiagnosis / Late Diagnosis

NTDT patients may develop iron overload if untreated

NTDT patients develop iron overload primarily due to increased gastrointestinal iron absorption.\(^2\)

β-thalassaemia intermedia patients have been shown to develop severe iron overload in the liver if left untreated.\(^4\)

Liver iron concentration (LIC) is associated with increased risk of complications in patients with β-thalassaemia intermedia.\(^3\)

9.0 mg/g dw Osteoporosis

7.0 mg/g dw Thrombosis Vascular complications

6.0 mg/g dw Pulmonary hypertension Hypogonadism Hypothyroidism Endocrine/bone complications

1.8 mg/g dw Normal LIC

NTDT complications increase with age if left untreated

<table>
<thead>
<tr>
<th>Condition</th>
<th>≤10 years</th>
<th>11-20 years</th>
<th>21-32 years</th>
<th>&gt;32 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg ulcers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholethiasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypogonadism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^5\)Musallam KM et al. Haematologica 2011;96:1605–1612
Pioneer success stories of the Southern Mediterranean
Example: Cyprus

Cyprus, Italy, Greece: The first countries to develop disease-specific policies within their national healthcare system.

Later followed by the UK and France.
Pioneer success stories of the Southern Mediterranean
Example: Greece

Fig. 1 Distribution of registered cases in the NRHG according to age groups. The peak of patient distribution corresponds to the age group of 36-45 years regarding TM, 46-55 years among TI, and 41-50 years among SCD patients. TM thalassemia major, TI thalassemia intermedia, HB1 hemoglobinopathy “IT”, SCA sickle cell anemia, S/β-thal double heterozygous HbS and β-thal.

Source: Voskaridou E et al, 2018
Before & After inclusion in the NHS – the example of the UK

2003: Community awareness, diagnosis & Standards of Care are integrated in the NHS

**Before inclusion in NHS:**

- 50% of thalassaemia major patients in UK die < the age of 35y

**After inclusion in NHS:**

- Survival estimates in Thalassaemia Major patients at UCLH

  - Source: Davis et al., UCLH Experience, 2001
  - Davis et al, 2001, UCLH Experience
  - N=103, 78% survival at 40 years
  - No death in cohorts after 1971
Successful National Control Programmes: Middle East
(consequent to inclusion of control programmes in national HC system)

Iranian National Prevention Programme Results

C = Actual Births

Carrier Rates of $\beta$-thalassaemia & HbS in EMRO

Bahrain – Falling SCD births (1985 – 2010)

Successful National Control Programmes: West Pacific

**Singapore – Decrease in births (1970 – 2016)**

**Number of β Thalassaemia Major Born**

[Graph showing trend in births]

**Hong Kong – Age Distribution**

[Bar chart showing age distribution of Thalassaemia patients in Hong Kong]

**Singapore – Increased survival (1970 – 2003)**

**Improved Survival of Thalassaemia Majors**

[Graph showing survival rates]

**Taiwan – Decrease in births (1987 – 2009)**

[Graph showing trend in births]

**Carrier Rates of β-thalassaemia & HbE in WPRO**

[Map showing carrier rates in various countries]
Successful National Control Programmes: South East Asia
Example: Thailand

COMMON THALASSEMIC DISORDERS IN S.E. ASIA

Hb H Disease
Homozygous β-Thal and β-Thal/Hb E

Asymptomatic Thalassemia
- α, and β-thalassemia trait
- Homozygous Hb E
- Homozygous Hb Constant Spring

Hb Bart’s Hydrops Fetalis

Thailand – Reduction in new births (nationwide)

Case Registration (year)

2000
- Integration of thalassemia program to existing health care system
- Dept of Health
- University
- R&D, Technical support
- Regional Health Center
- Co-ordination, Technical support
- General Hospital
- Complete service
- District Hospital
- Counseling, simple screening
- Community Hospital
- Counseling, transfer blood specimens
Diagnostic challenges

1. **Huge challenges** particularly in NTDT cases

2. **Contributing factors:**
   - [Table: Proportion of households with catastrophic health expenditure](#)
   - Consideration of total health spending in SEAR
     - **Comparison of total health spending in SEAR**

<table>
<thead>
<tr>
<th>Selected Asia Pacific countries</th>
<th>Percentage of households with catastrophic OOP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viet Nam</td>
<td>10.45%</td>
</tr>
<tr>
<td>Cambodia</td>
<td>5.02%</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>1.73%</td>
</tr>
<tr>
<td>Indonesia</td>
<td>1.26%</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>1.25%</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>1.21%</td>
</tr>
<tr>
<td>Thailand</td>
<td>0.80%</td>
</tr>
<tr>
<td>Philippines</td>
<td>0.78%</td>
</tr>
</tbody>
</table>

   *Defined as the incidence of household payments for health services exceeding 40% of net income after subsistence needs have been met.

   Source: WHO (2006a)

3. Lack of integrated disease-specific policies within UHC healthcare system, leading to undiagnosed / misdiagnosed cases with thalassaemia left out

4. High % of comorbidities leading to disabilities, and low quality of life for patients

Considering that thalassaemia is both **PREVENTABLE** and **TREATABLE**, this situation is **UNACCEPTABLE** and a violation of basic **HUMAN** and **PATIENTS RIGHTS** with costs to patient family, society, public health, economic development.
### Burden of Disease vs Prioritisation on Health Agendas

#### Recognition of the burden of haemoglobinopathies

- **WHO** recognises sickle cell disease as a worldwide public health issue.
- **UN** designates 19 June as World Sickle Cell Day.
- **WHO** adopts a resolution on the prevention and management of birth defects, including sickle cell disease.
- The American Society of Hematology (ASH) launches the Conquer SCD initiative.

#### Global Burden of Disease across all ages

<table>
<thead>
<tr>
<th></th>
<th>1990</th>
<th>2010</th>
<th>2013/2016/ heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sickle Cell Disease</strong></td>
<td>74th</td>
<td>70th</td>
<td>Burden unidentified</td>
</tr>
<tr>
<td>(Deaths/year)</td>
<td>17th</td>
<td>17th</td>
<td></td>
</tr>
<tr>
<td>(age group: 1-4 years)</td>
<td>28,640 (16756-40,869)</td>
<td>28,640 (16756-40,869)</td>
<td></td>
</tr>
<tr>
<td><strong>Thalassaemias</strong></td>
<td>65th</td>
<td>68th</td>
<td></td>
</tr>
<tr>
<td>(Deaths/year)</td>
<td>24th</td>
<td>24th</td>
<td></td>
</tr>
<tr>
<td>(age group: 1-4 years)</td>
<td>17,860 (15071-20430)</td>
<td>17,860 (15071-20430)</td>
<td></td>
</tr>
</tbody>
</table>

#### But... still largely neglected disorders

- The vast majority of patients with haemoglobinopathies live in low- and middle-income countries, where prevention and management programmes are usually lacking. For example, 79% of sickle cell anaemia births occurred in Sub-Saharan Africa in 2010.
- The life expectancy of patients with haemoglobinopathies is still considerably lower than that of normal individuals. For example, the life expectancy of patients with SCD is still shortened by ~2 decades compared to the general population.
- Drugs for patients with haemoglobinopathies are limited. For example, FDA only just approved the second drug to treat SCD since HU in 1970s.
Current Status of Prevention and Clinical Management for Thalassaemia globally
THANK YOU FOR YOUR ATTENTION

The face of thalassaemia

Then

Facial deformities
Minimally treated patients aged 8 and 20 (Cyprus, 1940s)

Now

Photos with permission (Modell and Berdoukas, 1984)