Thalassemia and other hemoglobinopathies among anemic individuals in Metro Manila: Preliminary findings from the National Nutrition Survey

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ILSI Southeast Asia region
Definitions

Anemia

• Insufficient amount of red blood cells to meet the body’s physiologic needs (hemoglobin)

• Hemoglobin cut-offs for adults (15+ yrs)
  – Males <130 g/L
  – Females <120 g/L

Iron deficiency

• Insufficient iron stores (serum ferritin)

• Most frequent cause of anemia

• Serum ferritin cut-offs (5+ yrs)
  – <15 ug/L (depletion)
  – >150-200 (risk of overload M & F, respectively)
Causes of anemia other than iron deficiency

- Other nutrient deficiencies
  - Folic acid
  - B12 (cobalamin)
  - Vitamin A
- Acute & chronic inflammation
- Parasitic infection (malaria, hookworm & other helminths)
- Thalassemias & other hemoglobinopathies

- Other infectious disease
- Chronic disease
- Gastric carcinoma
- Peptic ulcer disease
- Celiac disease
- Long-term use of aspirin or other NSAID
- Chronic kidney disease
- Maternal hemorrhage
- Other gynecologic disorders
- G6PD deficiency
Ranking of top causes of anemia in Southeast Asia 1990-2010 (Kassebaum et.al. 2014)

Adult females
- Iron deficiency
- Hookworm disease
- **Thalassemias**
- Malaria
- Uterine fibroids

Adult males
- Iron deficiency
- Hookworm disease
- **Thalassemias**
- Malaria
- Other tropical disease
A Parent with Thalassemia Minor

- Thalassemia Major
- Thalassemia Minor

A Parent with Thalassemia Minor

- Thalassemia Minor
- Normal Blood

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Genetic hemoglobin disorders (hemoglobinopathies)

Red blood cells
- Structurally abnormal (Hb variants)
- Inadequate amounts of hemoglobin chains (thalassemia)

Thalassemia (Microcytic hypochromic anemia)
Consequences of genetic Hb disorders

Severity of symptoms depends on severity of the disorder

- No symptoms (thalassemia trait)
- Mild to moderate anemia - slowed growth, delayed puberty, bone problems, enlarged spleen
- Severe anemia - pale & listless appearance, poor appetite, slowed growth, delayed puberty, jaundice, enlarged spleen, liver or heart, bone problems

Anemia is not amenable to dietary intervention
Disordered iron metabolism

- Excess free α-globin chains
- Denaturation and Degradation
- Formation of heme and hemichromes
- Iron-mediated toxicity
- Removal of damaged red cells

**Haemolysis**
- Increased erythropoietin synthesis
- Reduced tissue oxygenation

**Ineffective erythropoiesis**
- Anaemia

**Membrane binding of IgG and C3**
- Splenomegaly
- Iron overload

**Increased iron absorption**
- Erythroid marrow expansion
- Skeletal deformities, osteopenia
Liver iron concentration (LIC)

- Gold standard for measuring total body iron stores
In a study of people with NTDT, LIC increased 33% over a period of 13 years.

Source: Iron Health Alliance website
Clinical sequelae of iron overload

- Pituitary: impaired growth, infertility
- Thyroid: hypoparathyroidism
- Heart: cardiomyopathy, cardiac failure
- Liver: hepatic cirrhosis
- Pancreas: diabetes mellitus
- Gonads: hypogonadism
ILSI SEA - FNRI project

- Investigation of the occurrence of hemoglobinopathies among anemic individuals in the Philippines: Data from the 2013 National Nutrition Survey

- Consultant: Dr. Angelina Mirasol
Objectives

• To estimate the proportion of anemic individuals with nutritional iron deficiency vs. those with thalassemia/hemoglobinopathy

• To examine the factors that characterize anemic individuals with and without thalassemia (red blood cell indices, dietary intake, anthropometry, etc.)
Methods

• Cross-sectional survey
• Households in the National Capital Region (Metro Manila)
• Total number of individuals = 2145
• Age 6-59 y
• Number of anemic samples = 116 (5.4%)
• Hemoglobinopathies determined by capillary electrophoresis (Sebia Fully Automated Capillary Separation System)
Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity

WHO/NMH/NHD/MNM/11.1

Background

Anaemia is a condition in which the number of red blood cells (and consequently their oxygen-carrying capacity) is insufficient to meet the body’s physiologic needs. Specific physiologic needs vary with a person’s age, gender, residential elevation above sea level (altitude), smoking behaviour, and different stages of pregnancy. Iron deficiency is thought to be the most common cause of anaemia globally, but other nutritional deficiencies (including folate, vitamin B12 and vitamin A), acute and chronic inflammation, parasitic infections, and inherited or acquired disorders that affect haemoglobin synthesis, red blood cell production or red blood cell survival, can all cause anaemia. Haemoglobin concentration alone cannot be used to diagnose iron deficiency. However, the concentration of haemoglobin should be measured, even though not all anaemia is caused by iron deficiency. The prevalence of anaemia is an important health indicator and when it is used with other measurements of iron status the haemoglobin concentration can provide information about the severity of iron deficiency (1).

Scope and purpose

This document aims to provide users of the Vitamin and Mineral Nutrition Information System (VMNIS) with information about the use of haemoglobin concentration for diagnosing anaemia. It is a compilation of current World Health Organization (WHO) recommendations on the topic and summarizes the cut-offs for defining anaemia and its severity at the population level, as well as the chronology of their establishment.

The use of the cut-off points derived from the referenced publications permits the identification of populations at greatest risk of anaemia and priority areas for action, especially when resources are limited. They also facilitate the monitoring and assessment of progress towards international goals of preventing and controlling iron deficiency and further provide the basis for advocacy for the prevention of anaemia.
PRELIMINARY RESULTS
# Prevalence of anemia (Metro Manila, 2013)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Males</th>
<th>Females</th>
<th>Pregnant women</th>
<th>Total sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11</td>
<td>1.7</td>
<td>1.6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>12-14</td>
<td>1.7</td>
<td>4.0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>15 &amp; above</td>
<td>2.3</td>
<td>9.6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>2.2</td>
<td>7.8</td>
<td>33.3</td>
<td>5.4</td>
</tr>
</tbody>
</table>
## Severity of anemia

<table>
<thead>
<tr>
<th>Degree of anemia</th>
<th>6-11 y (%)</th>
<th>12-14 y (%)</th>
<th>15 y &amp; above (%)</th>
<th>All ages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mild</td>
<td>33.3</td>
<td>100.0</td>
<td>76.5</td>
<td>72.7</td>
</tr>
<tr>
<td>- Moderate</td>
<td>66.7</td>
<td>-</td>
<td>5.9</td>
<td>13.6</td>
</tr>
<tr>
<td>- Severe</td>
<td>-</td>
<td>-</td>
<td>17.6</td>
<td>13.6</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mild</td>
<td>66.7</td>
<td>75.0</td>
<td>58.2</td>
<td>59.3</td>
</tr>
<tr>
<td>- Moderate</td>
<td>33.3</td>
<td>25.0</td>
<td>34.2</td>
<td>33.7</td>
</tr>
<tr>
<td>- Severe</td>
<td>-</td>
<td>-</td>
<td>7.6</td>
<td>7.0</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Mild</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>62.5</td>
</tr>
<tr>
<td>- Moderate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25.0</td>
</tr>
<tr>
<td>- Severe</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12.5</td>
</tr>
</tbody>
</table>
Screening for thalassemia and hemoglobinopathies

- Full blood counts and haemoglobin electrophoresis
  - MCV (fL) >78
  - MCH (pg) >27
    - Hb electrophoresis
      - A + A₂ <3.2% F < 1%
        - Normal
      - A + A₂ <3.5% F < 1%
        - Iron studies
      - A + A₂ >3.5% F = 1 - 3%
        - β-Thalassaemia
      - A + A₂ >3.5% F ~ 1%
        - Co-existing α & β-Thalassaemia
      - A + A₂ <3% F = 5 - 35%
        - Intercellular distribution of Hb F
          - δβ-Thalassaemia
          - HPFH
          - Hb variant detected
          - Supplementary investigation: e.g. Sickle solubility, Heat stability, Inclusion bodies, etc.
          - Hb S, C, E
          - Others
  - MCV (fL) <78
  - MCH (pg) <27
    - Iron deficiency
    - Iron Replete
      - α-Thalassaemia
        - εγδβ-Thalassaemia
        - Mild β-Thalassaemia / Normal A₂

Figure 2. A guide to the diagnosis of the different forms of haemoglobinopathies in carriers (adapted from Cao et al., 2001).
## Distribution of abnormal Hb and IDA among anemic individuals

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Low MCV and low MCH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With hemoglobinopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Alpha thalassemia</td>
<td>7 (11.7)</td>
<td>14 (23.3)</td>
<td>21 (35.0)</td>
</tr>
<tr>
<td>- Beta thalassemia</td>
<td>2 (3.3)</td>
<td>3 (5.0)</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>- IDA concomitant HbE</td>
<td>-</td>
<td>1 (1.7)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>- Beta thalassemia, HbE interacting</td>
<td>-</td>
<td>1 (1.7)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td><strong>Total with hemoglobinopathy</strong></td>
<td>9 (15.0)</td>
<td>19 (31.7)</td>
<td><strong>28 (46.7)</strong></td>
</tr>
<tr>
<td>With iron deficiency anemia (IDA)</td>
<td>1 (1.7)</td>
<td>31 (51.7)</td>
<td><strong>32 (53.3)</strong></td>
</tr>
<tr>
<td><strong>B. Normal MCV and MCH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>In process</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Extent of iron stores based on serum ferritin concentration

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Depleted iron stores</th>
<th>Risk of iron overload</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Alpha thalassemia</td>
<td>16 (57.1)</td>
<td>-</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Beta thalassemia</td>
<td>2 (7.1)</td>
<td>-</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>IDA concomitant HBE</td>
<td>-</td>
<td>1 (3.6)</td>
<td>-</td>
</tr>
<tr>
<td>Beta thalassemia, HbE interacting</td>
<td>1 (3.6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>19 (67.9)</td>
<td>1 (3.6)</td>
<td>8 (28.6)</td>
</tr>
</tbody>
</table>
Implications for research

• Need to identify frequency of genetic Hb disorders and clarify their contribution to the burden of anemia in different geographic and demographic settings

• Need for screening surveys and micromapping studies to determine gene frequencies prior to implementing intervention programs

• Need to define optimal cut-offs for hemoglobin that define anemia in diverse populations, esp. where hemoglobinopathies are common

Reference: Parischa et.al. 2013. Control of iron deficiency in low- and middle-income countries.
Implications for iron supplementation and fortification policies

- Need to assess the safety of iron intervention programs in hemoglobinopathy carriers
- Need to assess risks vs. benefits of population-wide vs. targeted coverage of iron interventions
- Need to increase awareness of program planners and health workers regarding effects of iron in patients with thalassemia and abnormal Hb
THANK YOU