ANAEMIA IN CHILDREN – CHANGING TRENDS AND CLINICAL APPROACH

Quah Thuan Chong, Allen EJ Yeoh

In the past, most cases of anaemia in Singapore children were nutritional in origin. In 1963, Prof Wong Hock Boon in his paper “anaemias in Singapore children”, stated that 95% of all cases of anaemia seen in the Department of Paediatrics at that time were due to iron deficiency. There was not a single case of megaloblastic anaemia. In 1970, a 3-month prospective study showed that 6.4% of children admitted to the department had anaemia. All of them had iron deficiency, 76% had concomitant folate deficiency, and none had vitamin B12 deficiency. These children came from poor families, and the anaemia was mainly nutritional in origin. In 10%, hookworm infestation was found.

No other systematic studies on the epidemiology of anaemia in Singapore children have been done since then, but my impression is that nutritional anaemia has since then become very rare. This should not be surprising, as Singapore has become more affluent over these past 20-30 years, and malnutrition is very rare now - instead, we are now more concerned with overfeeding and obesity! Likewise, hookworm infestation is almost non-existent now in Singapore children.

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- Approach to anaemia
- Clinical example
- Laboratory diagnosis
- Therapy
- Conclusion

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APPROACH TO ANAEMIA

There are 2 different approaches that can be taken in determining the cause of anaemia in a particular child:

1. Pathophysiological approach
2. “Scenario approach”

The pathophysiological approach is a “scientific” one in which we examine the various possible causes of anaemia (Table 1). The “scenario approach” looks at the child as a whole, and assesses how likely he is to have a particular disease (Table 2). The latter requires knowledge of the social background of the child and the society in which he lives, combined with the present and past history. In real life, we usually combine the two approaches.

Table 1.
Causes of Anaemia (Pathophysiological approach)

<table>
<thead>
<tr>
<th>1. Deficient production</th>
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</thead>
<tbody>
<tr>
<td>• Nutrient deficiency (iron, folate etc)</td>
<td></td>
</tr>
<tr>
<td>• Aplasia/hypoplasia</td>
<td></td>
</tr>
<tr>
<td>• Marrow infiltration</td>
<td></td>
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<tr>
<td>• Renal failure</td>
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<td>2. Increased loss</td>
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<tr>
<td>• Bleeding (eg. GI bleed, menstruation)</td>
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<td>3. Increased destruction</td>
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<tr>
<td>• Haemolysis</td>
<td></td>
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<tr>
<td>• Hypersplenism (eg. Portal hypertension)</td>
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</table>

Table 2.
Anaemia in children: Scenario approach

- Age
- Social context
- Severity
- Tempo of disease
- Associated features (diarrhea, bleeding, etc)
- Family history (thalassaemia, Fanconi’s anaemia)
Clinical Example

I would like to illustrate these approaches, using as an example a one-year-old child whom we saw recently with severe anaemia, with a Hb of 4 g/dl (Table 2).

a. Age of Child
The age of the child is important, as there are problems specific to each age group eg infants who are weaned late may develop iron deficiency anaemia, usually towards the end of the first year. This may be a relevant factor in our patient, who is one year old. In older girls, a careful menstrual history is important, as the amount of blood lost through menstruation can occasionally be sufficient to cause iron deficiency.

b. Social Context
Even without further history or examination, we know that nutritional deficiency (so severe as to cause such a degree of anaemia) is unlikely in a Singapore child nowadays.

Important exceptions to take into consideration are:
- Very late weaning
- Takes a predominant goat's milk diet (we have seen a child who has severe concomitant iron and folate-deficiency anaemia due from this cause),
- Has peculiar food habits
- Vegetarian diet or food fads
- Has significant gastrointestinal problems (e.g. malabsorption)

The child was well grown, came from an upper-income family, and did not have unusual food habits.

C. Severity of Anaemia in Relation to Cause

Table 3.
Causes of Anaemia vs Severity

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderately severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Iron deficiency</td>
<td>- β-thalassaemia intermedia</td>
</tr>
<tr>
<td>- β-thalassaemia minor (trait)</td>
<td>- HbE-β-thalassaemia</td>
</tr>
<tr>
<td>- α-thalassaemia-1 (α0/α0 or αα/00)</td>
<td>- HbH thalassaemia</td>
</tr>
<tr>
<td></td>
<td>- Leukaemia</td>
</tr>
<tr>
<td></td>
<td>- Aplastic Anaemia</td>
</tr>
<tr>
<td></td>
<td>- Severe blood loss</td>
</tr>
</tbody>
</table>
There is of course some overlap among the different categories. For example, iron deficiency can present with any degree of severity. However, thalassaemia traits are always mild, unless there are other concomitant causes. Leukaemia in children is usually an acute disease, and so the anaemia is usually quite severe by the time the child seeks medical attention.

d. Tempo of Disease

*Despite the severe anaemia, the child was remarkably well, with no evidence of cardiac decompensation.* Thus, it is clear that her anaemia had been slowly developing over at least a few weeks, if not a few months.

e. Associated Features

*The child had no other features that we should look for in assessing anaemia (Table 4).*

<table>
<thead>
<tr>
<th>Table 4.</th>
<th>Associated Features to look for</th>
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</thead>
<tbody>
<tr>
<td>Fever (suggests leukaemia, aplastic anaemia)</td>
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<tr>
<td>Bleeding diathesis (leukaemia, aplastic anaemia)</td>
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<tr>
<td>Gastrointestinal bleeding (cow’s milk hypersensitivity, Meckel’s diverticulum/gastric ectopia)</td>
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<tr>
<td>Diarrhea (malabsorption)</td>
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<tr>
<td>Peripheral oedema (malabsorption)</td>
<td></td>
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<tr>
<td>Jaundice (haemolysis)</td>
<td></td>
</tr>
<tr>
<td>Failure to thrive (chronic disease eg. Renal failure)</td>
<td></td>
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<tr>
<td>Dysmorphic features (eg. Fanconi’s anaemia)</td>
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<tr>
<td>Purpura (leukemia, aplastic anaemia)</td>
<td></td>
</tr>
<tr>
<td>Organomegaly (liver, spleen – leukaemia, portal hypertension)</td>
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</tbody>
</table>

*In this child, apart from the pallor, there was mild pitting oedema. There was no other physical finding of note.*

f. Family History

The most common familial cause of anaemia, locally, is of course various kinds of thalassaemia. However, carriers are often asymptomatic, and thus it is not surprising that family history is often negative even in patients with thalassaemia.

However, we can do a “history stress test” i.e. probe deeper into the history to discover clues pointing to possible thalassaemia in the family. For example, the child's mother must have been pregnant before (!), and she almost certainly would have had a blood test. Was she told that she was anaemia? Better still, does she still have a copy of her FBC report? An unusually low MCV (< 70) would point towards the diagnosis of 0thalassaemia trait (the MCV in α-thalassaemia carriers is usually not remarkably low.)
The father would also have gone through National Service and had his blood tested, or gone for blood donation before. Was he told that he had anaemia, or had he ever been rejected for blood donation because of anaemia?

There was no family history of anaemia in this patient, even after the “history stress test”.

Laboratory Diagnosis

From the above, we would have a fair idea of the possible causes, and limit our investigations to the more relevant ones. In this particular patient, leukaemia, haemolysis and nutritional deficiencies are unlikely. It would be a waste of time and money, for example, to do routine marrow examination or assay the folate or vitamin B12 levels.

The most useful test in any case of anaemia is of course the full blood count (FBQ and peripheral blood film. Normal white blood cell counts, differential counts, and platelet counts, would help rule out serious diseases like leukaemia or aplastic anaemia.

The following is the FBC result of the patient:

\[ \text{Hb 4.5, WBC 11.2 (P 37, L 57, M 5, E 1), Plat 516, RBC 1.8, PCV 15.3, MCV 85, MCH 25, MCHC 29.4.} \]

Peripheral blood film showed: Slight polychromasia, moderate hypochromia and anisocytosis and microcytosis.

Reticulocyte count was 6.5%.

RBC indices are very helpful. Microcytic anaemia is common and is almost always due to either iron deficiency or thalassaemia. The problem in paediatrics is that the MCV (mean corpuscular volume) varies with age. A rule-of-thumb is that the lower limit of MCV is 70 + age (in years). Thus, an MCV of 76 is within normal limits for a young child, but considered as decreased for a child > 6 years of age.

In this child, the MCV appeared to be normal. However, the PBF showed many microcytes. Thus, the normal MCV is misleading - the microcytosis is masked by a brisk reticulocyte response. This response is most likely explained by the fact that a private practitioner had just given her iron. Examination of the blood film showed a typical iron-deficiency picture. This was confirmed by a low serum ferritin level.

At this point, I would like to say a few words about laboratory diagnosis of iron deficiency. Serum iron and transferrin levels are often done to assess iron deficiency. However, the best single test in most cases is a serum ferritin level, which is more sensitive and specific. The drawback of serum ferritin is that the level can be increased.
in the presence of an infection. So, it may be wise to check the level only after resolution of any infection.

**Therapy: iron deficiency is much more than a blood problem**

As the child was not in distress, we decided against blood transfusion. She was given oral iron therapy. Within 24 hours, she became much more alert and active. Within one month, the Hb rose from 3.6g/dl to 10.6g/dl. She would continue to receive iron replacement for another 2-3 months to replenish her body stores of iron, and her Hb level would be monitored to see whether there is a recurrence of anaemia. If so, further investigations would be necessary to look for potential sources of blood loss.

At this point, a question may have occurred to you: how could she have become “much more alert and active” within 24 hours, when “we all know” that the Hb takes some time for the anaemia to improve (an increase of 1 g/dl after one week of iron therapy). This takes us to another lesson: iron deficiency is much more than a blood problem. Iron is an essential component of many essential enzymes and co-enzymes in the body (e.g. cytochromes, myoglobin, catalase, xanthine oxidase).

Thus, the rapid clinical response is probably due to replenishment of iron store in these important molecules, and this is an additional piece of evidence of the important role of iron in the body.

Iron deficiency has also been shown to be associated with intellectual impairment, which may be irreversible even after iron replenishment. Therefore it is important for us as doctors to diagnose iron deficiency early in our patients, and to treat them early.

**A Twist in the Tale**

Having diagnosed iron deficiency anaemia, it is imperative to investigate the cause of this deficiency. Apart from a nutritional cause, occult bleeding needs to be excluded. Stools should be examined for blood. *In this patient, stool examination was positive for occult blood.*

*In view of the presence of oedema, the patient's serum albumin was measured, and she was found to have hypoalbuminaemia. This combination of iron deficiency anaemia and hypoalbuminaemia has been reported in cow's milk protein hypersensitivity (non-IgE mediated), where there is occult blood loss and a protein-losing enteropathy. Both respond well to a non-cow's milk diet and iron therapy. In this patient, stool for occult blood was positive. *In view of the possibility of cow's milk protein hypersensitivity, cow's milk was stopped and the patient did very well with resolution of oedema.*

A close watch has to be kept on this child to make sure that no other source of bleeding has been missed.