CLINICAL INVESTIGATIONS FROM THE RACP

The pale child

Remember the basics and keep it simple

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Isolated pallor is common in children, either as a primary presentation or an incidental finding. A simple clinically-based approach can often make diagnosis and management of the pale child straightforward. A careful history and clinical examination will frequently lead to the underlying diagnosis of anaemia, and assessment of vital signs and consideration of the acuity of the anaemia ensures the safety of the patient.

The child presenting with pallor is a common clinical problem. Sometimes paleness is the primary purpose for clinical presentation, and at other times it is noticed in a child presenting for other reasons.

Paleness of skin is a nonspecific feature that might be part of numerous infective, inflammatory or painful conditions, or indeed part of a normal complexion. Pallor of the lips or mucous membranes and palmar creases usually reflects anaemia and should alert the clinician to consider several important conditions. Pallor in the setting of fever, bruising or petechiae with or without limb pain should instantly raise the possibility of childhood leukaemia or rarer causes of bone marrow failure.

Isolated pallor, however, is common, and the purpose of this paper is to review a simple clinically based approach to the pale (anaemic) child that can often make diagnosis and management of such children straightforward.

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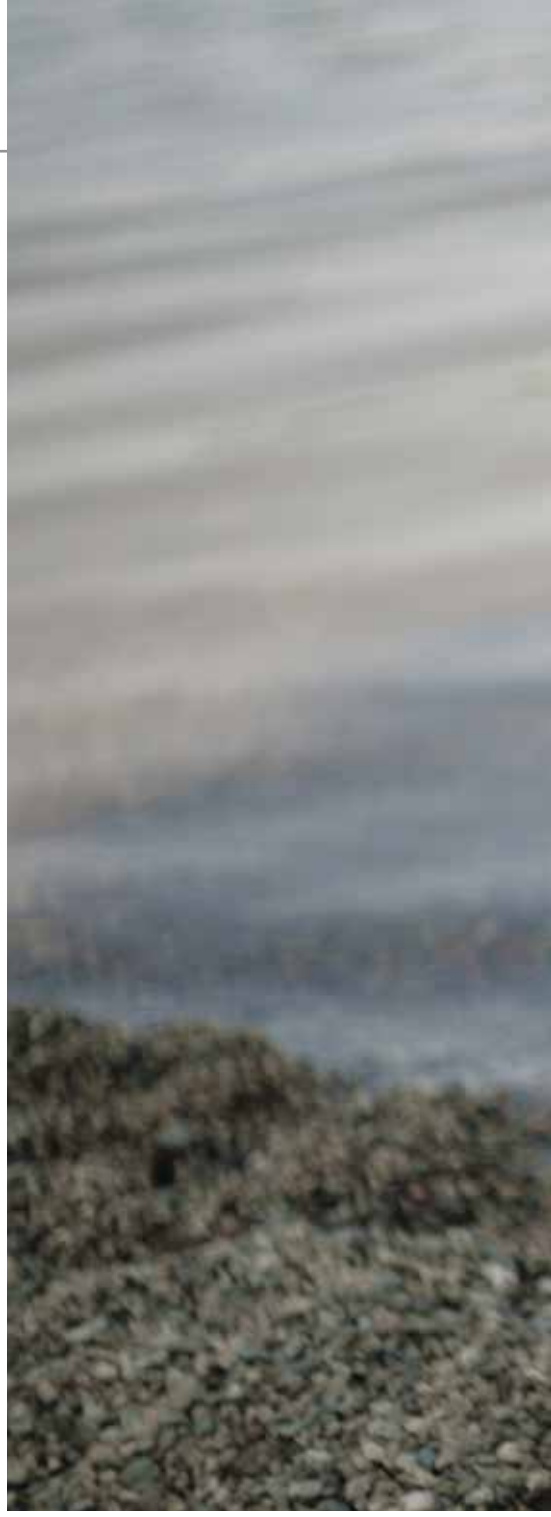

Defining anaemia

Anaemia is defined as a haemoglobin concentration and/or red cell count below that which is normal for age and gender. Haemoglobin concentration provides a more direct measure of anaemia than does red cell count.

Because the normal concentration range for haemoglobin varies considerably with age, knowledge of what is normal is imperative for accurate diagnosis of anaemia.

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KEY POINTS

- Children are pale for many reasons but true pallor of the mucous membranes and palmar creases usually represents anaemia.
- There are many causes of anaemia. Arriving at the appropriate clinical response is usually straightforward if the process is broken down into a few simple decisions.
- Acute anaemias, such as acute blood loss or haemolysis, are medical emergencies and almost always require immediate transfer of the patient to hospital, potentially for transfusion support.
- The haemoglobin level is never the determinant of the need for transfusion. Rather, it is the ability of the cardiovascular system to maintain oxygen delivery.
- Chronic anaemias, especially iron deficiency, are often well tolerated and have minimal symptoms, but the long-term effects are significant, so a high index of suspicion is appropriate.
- Iron deficiency is easy to treat in principle but often much more difficult in practice, requiring considerable time and effort to help parents with toddler behaviour and appropriate dietary patterns. Simply prescribing iron supplements is inadequate.
- Megaloblastic anaemia is insidious in its presentation and has potential marked impact on long-term neurodevelopmental outcome. It should be considered early in children with neurodevelopmental delay, failure to thrive and abnormal haematology.

Clinical presentation of anaemia

Underlying physiological principles

Consideration of the underlying physiological principles is important when thinking about the clinical presentation of anaemia and the initial clinical assessment. The prime purpose of haemoglobin is as an oxygen delivery mechanism. The ability to deliver oxygen to all organs of the body, but particularly the brain, is fundamental to the survival of any complex organism. The amount of oxygen delivered at any given time is determined by the tissue oxygen delivery equation:

Tissue oxygen delivery (mL/min) = cardiac output (L/min) x haemoglobin concentration (g/L) x oxygen saturation (%) x 1.34 mL/g

(where the constant 1.34 mL/g is the amount of oxygen per gram of normal haemoglobin).

Cardiac output is the product of heart rate and stroke volume, and given that stroke volume rarely changes acutely, the

1. CLASSIFICATION OF ANAEMIA BY AETIOLOGY: A SIMPLISTIC FRAMEWORK

- Failure of production of red blood cells
- Increased destruction/loss of red blood cells
- Ineffective production of red blood cells

cardiac compensation for rapid loss of haemoglobin is reflected in the heart rate. Children with more slowly developing anaemia (such as iron deficiency) may have a very low haemoglobin concentration without a particularly elevated heart rate, as there has been time for stroke volume adjustment. Therefore the level of haemoglobin at which there is cardiac decompensation differs based on the speed at which the anaemia has developed, and hence the absolute level of haemoglobin is never the only determining factor when deciding on aggressiveness of therapy. For example, transfusion decisions (the decision to transfuse or not, and also the urgency of transfusion) should never be based on a patient's haemoglobin concentration alone; the patient's ability to deliver oxygen and to cope with the additional demands being made on their cardiac output should also be considered.

Children with chronic hypoxia (e.g. congenital cyanotic heart disease) will compensate by increasing their normal haemoglobin levels, and have a relative polycythaemia. In these children, a haemoglobin level that might otherwise be considered normal in an acyanotic child may be low enough that transfusion is required to maintain adequate oxygen delivery.

Another important point to note is that the equation involves oxygen saturation (SaO_2) and not arterial partial pressure of oxygen (PaO_2). Thus oxygen therapy is of little use to a patient who has reduced haemoglobin in the absence of concurrent lung disease, as the haemoglobin they do have is usually 100% saturated.

In the absence of fever (which will increase the heart rate) the heart rate is effective for monitoring the progress of an anaemic patient acutely, as it will increase or decrease in an inverse linear relationship with the haemoglobin concentration.

Knowing the vital signs is, therefore, a mandatory part of the clinical assessment of any patient suspected of anaemia, especially acute blood loss or haemolysis where rapid changes are likely.

Symptoms

The symptoms of anaemia predominantly reflect the symptoms of raised cardiac output, as discussed above. Pallor is arguably the only symptom directly related to the anaemia. Tiredness and lethargy, or in more extreme cases, signs of heart failure such as oedema and breathlessness, are more features of the increased demands on cardiac output. Clinical signs of hypoxia such as disorientation, confusion and air hunger occur only in extreme cases.

If local vascular beds have flow impediments then local signs of hypoxia (stroke, myocardial infarction) are common, although less so in children than in adults. In infants and toddlers, the inability to further increase cardiac output is often reflected in poor feeding (the most energetic activity for babies) and, in the longer term, failure to thrive. Older children may describe exercise intolerance or exercise-induced palpitations. Parents of many children with chronic anaemia will describe nonspecific irritability, poor sleeping, poor concentration and learning difficulties; whether this reflects direct impact of reduced oxygen delivery to the brain or the underlying cause of the anaemia, especially if related to haematinic deficiency, is not always clear. Other symptoms are usually related to the underlying cause of the anaemia and will be discussed subsequently.

Classifying anaemia

There are numerous different ways of classifying anaemia, and in simple terms the aetiological classification as described in Box 1 is a useful way to consider the possible causes. However, from a diagnostic and clinical care perspective the most important classification initially is to determine whether the anaemia is regenerative (acute blood loss or destruction; e.g. haemolytic anaemias) or aregenerative (failure of production; e.g. iron deficiency anaemia). Regenerative anaemias have the potential for rapid decrease in haemoglobin concentrations and acute decompensation and death. Hence children with these anaemias require urgent attention and frequently urgent intervention (transfusion).

Although conditions causing ineffective production are often a combination of regenerative and aregenerative anaemia, in terms of each clinical presentation, usually one form is dominant and so the classification of each clinical episode can be dichotomous.

Regenerative anaemia

Acute blood loss should be relatively easy to determine on history and examination, although occasionally the blood loss is occult into an expandable body cavity. In contrast, chronic blood loss tends to present more as an aregenerative anaemia (iron deficiency) and can be much more difficult to detect.

In children, the clinical features suggestive of a regenerative anaemia such as a haemolytic anaemia are often a short history, with or without an intercurrent infection. There may be a known inherited haemolytic anaemia in the background or the patient may lack any prior history. Jaundice in combination with pallor is a common feature in haemolysis, although the serum bilirubin has to increase to at least 60 μmol/L before icteric sclera can be clinically detected. 'Bloody' or very dark coloured urine (haemoglobinuria) is usually associated with intravascular haemolysis and usually signifies florid haemolysis. Splenomegaly may or may not be present (common in children with hereditary spherocytosis). Initial investigations should include a full blood count and blood film examination, serum

TABLE 1. INTRINSIC RED CELL CAUSES OF HAEMOLYSIS

Site of problem in red cell	Conditions			Features			
	Most common	Less common	Rare	Causes jaundice at birth	Causes intermittent haemolysis during childhood	Blood film features of common abnormality during acute haemolysis	Intravascular haemolysis
Membrane	Hereditary spherocytosis	Hereditary pyropoikilocytosis	Xerocytosis* Paroxysmal nocturnal haemoglobinuria†	Common	Common	Spherocytes	No
Haemoglobin	Sickle cell disease or thalassaemia	Unstable haemoglobin disease	Haemoglobin M disease (methaemoglobin)	Rare	Common	Sickle cells (sickle cell disease), target cells Hypochromic microcytosis (thalassaemia)	Yes
Enzyme	G6PD deficiency	Pyruvate kinase deficiency	Other enzyme deficiencies	Common	Common	Blister and bite cells	Yes

Abbreviation: G6PD = glucose-6-phosphate dehydrogenase.

* Very rare.

† An acquired clonal disorder that is rarely seen in children (occasionally in teenagers). The other intrinsic disorders are all inherited and present far younger.

bilirubin level and reticulocyte count to confirm the presence or absence of haemolysis. In young children, additional investigations such as haptoglobin and lactate dehydrogenase levels rarely add to the diagnostic algorithm and are not helpful.

Having decided that the patient has haemolysis (presence of anaemia, reticulocytosis and jaundice), the next concern is the severity of the haemolysis. Constant assessment of the heart rate and the haemoglobin level is required to determine this. In general, any child presenting with haemolysis should be admitted to hospital and monitored closely until the tempo of the haemolysis is understood, irrespective of the initial haemoglobin measurement. Transfusion support is the mainstay of treatment for patients with acute haemolysis, and early transfusion is usually sensible. Transfusion should never be delayed because of diagnostic uncertainty.

Often the investigations for the potential cause of the haemolysis can be carried out simultaneously with the investigations to prove haemolysis is present, based on the degree of clinical suspicion (a pale, jaundiced, tachycardic child is usually suspicious enough).

Investigating the causes of haemolysis

Regarding the causes of haemolysis, the easiest classification is to consider causes intrinsic to the red cells and causes extrinsic to the red cells. Intrinsic and extrinsic causes, their features and, for extrinsic causes, diagnostic tests are listed in Tables 1 and 2. A few specific causes are discussed in more detail later.

The processes that cause intravascular haemolysis as distinct from extravascular haemolysis (e.g. splenic destruction) are useful to consider as they can be associated with free plasma haemoglobin, which can block kidneys (or cause haemoglobinuria) and hence require adequate hydration. They can also lead to the measured haemoglobin being higher than the actual oxygen-carrying haemoglobin (intracellular haemoglobin) as analysers cannot tell if the haemoglobin they measure is from plasma or red cells, with the result that patients can be considerably more hypoxic than might be expected for the measured haemoglobin, and hence need more aggressive transfusion support.

For causes intrinsic to red blood cells, the blood film is useful in guiding subsequent investigations. If hereditary spherocytosis is suspected, the traditional osmotic fragility testing is now mostly replaced by the eosin-5-maleimide binding test, a relatively specific flow cytometry test (approximate sensitivity 90% and specificity 95%) that can be performed on less than 0.5 mL of blood, including capillary samples, within hours. If haemoglobin problems are suspected, a rapid sickle cell test (using light microscopy) or haemoglobin electrophoresis are usually diagnostic. If unstable haemoglobins are suspected, either heat instability or isopropanol testing is required. If glucose-6-phosphate dehydrogenase (G6PD) deficiency is suspected then G6PD assay is the most useful test. It may be falsely normal during acute

TABLE 2. EXTRINSIC CAUSES OF HAEMOLYSIS

Extrinsic cause	Pathophysiology	Blood film features in acute haemolysis	Diagnostic tests	Intravascular haemolysis
Immune	Warm (IgG) Cold (IgM) Paroxysmal cold haemoglobinuria (PCH)	Spherocytes (IgG) Agglutination (IgM)	Direct antiglobulin test	IgM and PCH only
Microangiopathic	Mechanical intravascular hardware Haemangioma Disseminated intravascular coagulation (DIC) Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome (TTP/HUS)	Red cell fragmentation Thrombocytopenia (DIC, TTP/HUS)	–	Yes
Infective	Malaria	Parasitaemia	Thick and thin films Rapid diagnostic tests (antigen tests)	Yes
Metabolic	Wilson's disease	Acanthocytes	Serum caeruloplasmin	Yes

haemolysis because reticulocytes have higher levels of G6PD, even in deficient patients. Investigation for less common and rare causes is usually fruitless in the acute setting, and these can be diagnosed in the fullness of time.

The blood film is also useful in guiding subsequent investigations for causes extrinsic to red blood cells. For these causes, a direct antiglobulin test (also known as Coomb's test) is warranted in almost all first presentations of haemolysis to exclude immune causes. Some drugs may cause immune haemolysis (as well as precipitate haemolysis in children with G6PD deficiency) so a drug history is important in all children with haemolysis. Microangiopathic causes need only be investigated in the presence of red cell fragmentation on the film. Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome usually occurs in association with other clinical features, including renal or neurological symptoms. Disseminated intravascular coagulation is usually seen in very sick children, and is most commonly precipitated by sepsis. Wilson's disease rarely presents as primary haemolysis and pre-existing liver disease is more common. Malaria should be preceded by a history of travel to an affected area.

In summary, the useful investigations in the acute setting should be guided by the blood film appearances but a direct antiglobulin test is always required. Immune-mediated haemolysis can often be particularly aggressive and IgG-mediated haemolysis will benefit from corticosteroid therapy; therefore this should never be missed. The eosin-5-maleimide binding test, G6PD assay and haemoglobin electrophoresis are also reasonable front-line investigations. Relevant investigations for the remaining extrinsic causes should be guided by appropriate details on history and examination. Further investigations for rarer causes should generally be left until a later date. This is because waiting for initial investigation results to be negative before embarking on more comprehensive investigation delays transfusion, and all-inclusive investigation at initial presentation prior to transfusion wastes time and resources as the most common causes are covered by the simple investigations detailed above.

Specific causes of haemolysis in childhood

Hereditary spherocytosis

Hereditary spherocytosis is a common disorder, and is autosomal dominant (70%) or autosomal recessive (30%). Patients usually have chronic compensated haemolysis with acute exacerbations related to viral illness. Parvovirus can induce aplastic crisis. Splenomegaly is usually clinically detectable after the age of 12 months, and the spleen can get quite large. Gallstones are common at a young age. Definitive treatment is splenectomy, but this is often not clinically indicated in children.

Hereditary pyropoikilocytosis

Hereditary pyropoikilocytosis is an uncommon to rare disorder that usually presents in neonatal life with jaundice, anaemia and a characteristic blood film with marked poikilocytosis.

Unstable haemoglobins

Unstable haemoglobins are uncommon to rare causes of haemolysis. Patients usually have a chronic compensated haemolysis with acute exacerbations.

G6PD deficiency

G6PD deficiency is caused by a single gene mutation. Although an X-linked condition, girls often present with clinically significant haemolysis as well. Neonatal jaundice is common.

Children with G6PD deficiency mostly present with classic favism (i.e. severe haemolysis on exposure to fava beans, also

TABLE 3. CLASSIFICATION OF ANAEMIA BY RED CELL SIZE

Cause of anaemia	Red cell size		
	Microcytic	**Normocytic**	**Macrocytic**
Haematinic deficiency	Iron deficiency anaemia	Mixed deficiency anaemia	Anaemia due to vitamin B_{12}/folate deficiency
Ineffective production*	Thalassaemia Sideroblastic anaemia	Sickle cell disease	Dyserythropoiesis
Toxin	Lead poisoning anaemia	–	Anaemia due to many drugs
Systemic disease	Anaemia due to chronic disease/renal disease	Anaemia due to chronic disease/renal disease	Anaemia due to liver disease
Aplasia	–	Diamond–Blackfan anaemia Transient erythroblastopenia of childhood (TEC)	Inherited bone marrow failure syndrome, e.g. Fanconi's anaemia

* Ineffective production problems frequently present as haemolysis.

known as broad beans). Families should be reassured that all other beans and vegetables are safe, and unjustified dietary exclusions should be avoided. Naphthalene is another known precipitant and clothes previously stored with naphthalene moth balls should be avoided. Some specific drugs and chemicals are also precipitants and should be avoided, however this is a much shorter list than often publicised on websites about G6PD deficiency.

Parental education about appropriate response to acute pallor, jaundice or lethargy is critical, as is true for all haemolytic anaemias. This should be a major aim of follow up after any acute episode.

Pyruvate kinase deficiency

Pyruvate kinase deficiency is an uncommon autosomal recessive cause of haemolysis. Neonatal jaundice is common and a chronic haemolysis, either compensated or occasionally transfusion-dependent, usually ensues.

Autoimmune haemolytic anaemia

Autoimmune haemolytic anaemia (AIHA) is common in children, but unlike in adults is most often an isolated phenomenon. Warm AIHA (mediated by IgG autoantibodies against red blood cell surface antigens that are most active at 37°C) is most often precipitated by nonspecific viral infection and is corticosteroid-responsive. Hence a direct antiglobulin test in any patient with haemolysis is important if the diagnosis is not known. Treatment is with oral prednisolone, and 1 mg/kg/day is the usual starting dose. The duration of therapy and the weaning strategy are somewhat dependent on the response to therapy and the ongoing transfusion requirements.

Cold AIHA (mediated by IgM antibodies most active below 30°C) is most commonly associated with *Mycoplasma pneumoniae* infection. Corticosteroid therapy is of no value and so the treatment of choice is transfusion support alone, similar to all the hereditary haemolytic diseases.

Therapy for haemolysis

Immediate therapy for children with haemolysis is usually transfusion support, with the frequency and volume of transfusions being guided by the heart rate and the haemoglobin levels as well as the clinical behaviour of the child. Multiple transfusions may be required, and also, in most cases, a stable haemoglobin level for longer than 24 hours before discharge from hospital. Folate supplementation is often given after acute episodes. Treatment of any intercurrent precipitating illness is also appropriate. In cases of intravascular haemolysis, adequate hydration and monitoring of renal function is relevant.

Haemolysis in a child should never be underestimated. Decreases in haemoglobin concentration can be precipitous, and children can tolerate anaemia well but then decompensate quickly. Haemolysing children identified in the community should be investigated and followed closely; almost all will require admission to hospital.

Aregenerative anaemia

Aregenerative anaemias represent failure of production. Bone marrow failure in a broader sense (pancytopenia) needs to be considered separately and will often require bone marrow examination to exclude leukaemia or aplastic anaemia. For isolated anaemia, once a regenerative anaemia has been excluded (normal bilirubin level and normal or reduced reticulocyte count) then classification of the anaemia based on red cell size is often the next helpful step to determine appropriate investigations (Table 3).

Nutritional anaemias

The nutritional anaemias are common and important and deserve some specific discussion.

Iron deficiency anaemia

Iron deficiency is the most common nutritional deficiency in the world, mainly affecting infants and women. In many parts of the world this relates to intestinal worm infestations, but in Western societies, diet deficiency is the major cause of iron deficiency in children. Apart from the effects of anaemia per se, iron deficiency may be associated with long-term neurological, developmental and behavioural effects, and has been linked to poorer cognitive and motor function, including lower development assessment scores as well as socioemotional behaviour difficulties. Children with iron deficiency can present with pica (a desire to eat nonfood items such as paper, dirt, plastic and ice). Parents often describe nonspecific irritability, sleep disturbance and concentration or learning issues, all of which resolve rapidly on iron supplementation, independent of any changes in haematological parameters.

Early identification and aggressive treatment of iron deficiency is therefore crucial. A high index of suspicion should be maintained for iron deficiency, and opportunistic dietary history screening should be performed on all children presenting for medical intervention.

In Western society, term infants are almost never iron deficient during the first six months of life without iatrogenic blood loss. Both breast milk and formula, most of which are iron fortified, are suitable for infants' iron needs. Standard cow's milk, goat's milk and soy milk have low iron content and should not be offered to infants less than 12 months old. By around 6 months of age, infants should be weaned onto iron rich solids; most early infant foods, like infant cereals, are iron fortified. Children who fail to transition to solid foods around the age of 6 months, who continue with breast milk or formula intake greater than 600 mL per day after 12 months of age or who commence cow's milk before 12 months of age should all be suspected of being iron deficient and screened with full blood examination (FBE) and a ferritin level. This screening should be performed even in the absence of symptoms, as the long-term developmental effects are independent of the presence or absence of anaemia and relate to the iron deficiency. Of note, measuring the serum iron level is not a helpful investigation for screening or diagnosing iron deficiency as serum iron concentration is subject to considerable diurnal variation and reflects immediate iron intake; it is, however, useful for checking compliance to iron therapy or for investigating possible iron overdose. In well children, the only useful test to determine iron deficiency is the serum ferritin, not withstanding that it is an acute phase reactant that can thus be normal in acute infections even in the presence of true iron deficiency. If the history is strongly suggestive of dietary iron deficiency, then commencement of iron therapy with only a baseline FBE is not unreasonable. Alternatively, the child can be reassessed when any acute infection has settled and the ferritin level measured.

Apart from infants as described, the other common group in whom iron deficiency is noted is menstruating teenage girls. Again, based on menstrual history and FBE alone, it is often not unreasonable to commence iron therapy and dietary improvement without further testing at initial presentation.

Children other than infants, toddlers and teenage girls who present with iron deficiency should be investigated for potential causes of malabsorption or chronic blood loss.

The major differential diagnosis is thalassaemia trait, and the red cell count (often elevated in thalassaemia minor and reduced in iron deficiency) may give a clue. The two conditions frequently coexist. If iron deficiency is suspected, treatment with iron prior to testing for thalassaemia is reasonable as iron deficiency can affect interpretation of beta thalassaemia testing.

The principles of therapy for iron deficiency anaemia are given in Box 2.

Anaemia due to vitamin B_{12} or folate deficiency

Megaloblastic anaemia in childhood is a rare but important condition, and in the young infant age group, marked neurological impairment is common and delays in diagnosis can significantly worsen the long-term neurodevelopmental outcome. Urgent recognition and intervention is therefore important.

Dietary sources of vitamin B_{12} include meat, fish, dairy products and eggs; as it is not found in plants, strict vegans readily become deficient without supplementation. Folate is present in many foods, of both plant and animal origin, but substantial losses can occur during cooking and storage. Dietary deficiency of folate is rare in children unless they are fed on goat's milk alone, which is deficient in folate. Goat's milk-based formulas are supplemented with folate and therefore not a problem.

Vitamin B_{12} deficiency is far more common than folate deficiency in children, yet still probably rare. From a dietary perspective, the most common cause is maternal vitamin B_{12} deficiency in breastfed babies. The mother may be deficient because of her diet or because of undiagnosed pernicious anaemia or other causes of malabsorption. Non-diet-related causes in infants include transcobalamin II deficiency (autosomal recessive) or abnormalities of the vitamin B_{12} metabolic pathways.

The combination of neurological regression, failure to thrive and any haematological abnormality in a child under 18 months of age should raise the

2. PRINCIPLES OF THERAPY FOR IRON DEFICIENCY ANAEMIA

Blood transfusion

Blood transfusion is rarely necessary and should only be given when there is an urgent need to replace oxygen-carrying capacity in severe decompensated anaemia.

Oral iron therapy

Full replacement of iron stores with oral iron therapy for three months is essential. Recommended dosing (in terms of elemental iron) is 3 to 6 mg/kg/day in two or three divided doses daily. Iron is best administered on an empty stomach, with absorption enhanced by taking with fruit juice high in vitamin C. Iron absorption is inhibited by tannins (tea) and calcium (milk), and oral iron therapy should not be taken with either of these. An oral liquid iron preparation is available, containing 6 mg elemental iron per mL; 1.0 mL/kg is the maximum recommended daily dose.

Indications for intravenous iron include: contraindications to oral iron such as inflammatory bowel disease, poor compliance or tolerability of oral iron preparations, malabsorption, chronic renal disease requiring erythropoiesis-stimulating agents, ongoing iron losses that exceed iron absorption such as gastrointestinal bleeding or menorrhagia.

Treatment of the underlying cause

Treatment of the underlying cause (dietary, menstrual loss, other) is required to prevent relapse. This is often the most difficult part when treating iron-deficient children. Toddlers who love their milk, for example, are often very resistant to change and it can take considerable coaching and support of parents to effect the behavioural changes required to develop good iron dietary intake. Failure to provide this support inevitably leads to failure of resolution or relapse of the iron deficiency, which often precipitates further unnecessary investigations and much anxiety. Girls with menorrhagia first need management of their menstruation to reduce the blood loss; there are several options for this (e.g. hormonal treatment, tranexamic acid).

After commencement of oral iron therapy, there is usually an immediate improvement in any behavioural components. In terms of resolution in haematological parameters, the following is the normal response to therapy:

- reticulocytosis is often seen after three to five days of therapy and is useful for ensuring normal absorption of iron and compliance with therapy
- haemoglobin level is usually two-thirds back to normal after three weeks of therapy and fully normalises within two months
- mean corpuscular volume normalises within three months of therapy commencement; a failure to do so may indicate a coexisting thalassaemia minor
- serum ferritin level should be normal by the end of three months of therapy.

Documentation of initial adequate response and full resolution of iron deficiency is important, but the frequency of testing during the treatment period depends on the clinical situation and compliance. Once three months of therapy is completed, and the FBE and serum ferritin level are documented as normal, most children should continue to be followed for another 12 months with two to three further measurements of FBE and serum ferritin level to ensure there is no relapse. Relapsed patients usually require more extensive investigation because the relapse may be due to failure of dietary correction or the presence of an unrecognised cause of iron malabsorption or iron loss (e.g. coeliac disease, inflammatory bowel disease), rather than poor compliance.

Abbreviation: FBE = full blood examination.

possibility of megaloblastosis and lead to urgent investigation and treatment. The neurological symptoms can include loss of developmental milestones such as smiling, vocalisation, head control and purposeful movements, as well as reduced or increased tone and seizures and abnormal movements ranging from jitteriness to true choreoathetoid movements. The systemic symptoms may include failure to thrive, weight loss, gastrointestinal dysfunction, skin rashes, glossitis and mouth ulceration.

The development of these symptoms is often slowly progressive over months. It is not uncommon for children to have presented on multiple occasions for medical assessment, with mothers often stating that something is wrong with their baby but they cannot put their finger on it, before the diagnosis is eventually made.

Megaloblastosis is one of the few reversible causes of neurological regression in infancy, hence the need for a high index of suspicion. As the long-term outcome appears to be related to the depth of deterioration reached, early diagnosis and treatment offers a far better prognosis.

The initial FBE gives the clues: macrocytosis, hypersegmented neutrophils and varying degrees of cytopenias. Any cell line may be more or less affected. Measurement of serum vitamin B_{12} level and demonstration of intracellular deficiency of vitamin B_{12}, which is achieved by showing elevated serum homocysteine levels and/or elevated urinary methyl malonic acid, is required to confirm the diagnosis.

Replacement therapy should be initiated as soon as possible. Delays of hours can potentially make a difference to the long-term neurological outcome. For vitamin B_{12} deficiency, the treatment is 1000 µg hydroxocobalamin intramuscularly daily for the first week, until the cause of the vitamin B_{12} deficiency is known and a longer term plan can be made. Cyanocobalamin should be avoided as it is ineffective in some of the metabolic causes. For folate deficiency, 5 mg oral folate daily can be given, until sufficient modification to the dietary intake has been made. Many clinicians treat with both vitamins to avoid the potential for missing combined deficiency and because there are likely no ill effects from doing so. Most children will need long-term developmental follow up.

Transient erythroblastopenia of childhood

Transient erythroblastopenia of childhood (TEC) is a relatively common and self-limiting normochromic normocytic anaemia of unknown aetiology. Although parvovirus is a known cause of red cell aplasia in children with underlying haemolytic disease, it has no role in the aetiology of TEC.

TEC classically presents as a child aged over 1 year who is pale but otherwise well. The blood film shows normochromic normocytic anaemia typically with no other abnormalities, although there may be another mild cytopenia. The anaemia may be severe, and transfusion support may be required until spontaneous recovery occurs, usually within a couple of months. On examination, only signs of anaemia are found. Occasionally the child presents in the recovery phase when there is a reticulocytosis, but there should never be jaundice.

The differential diagnosis is congenital red cell aplasia, eponymously called Diamond–Blackfan anaemia (DBA). Distinguishing the two conditions clinically can be challenging, although most cases of DBA present before 1 year of age. The red cell adenine deaminase level is abnormal (elevated) in children with DBA, and this is the most sensitive diagnostic test for the condition. As DBA can respond to corticosteroids, making the diagnosis accurately is important. Children with DBA require subspecialist paediatric haematology care.

Conclusion

The pale child is a common clinical presentation, either as an incidental finding or as the primary presenting complaint. Careful history and clinical examination will frequently lead to the underlying diagnosis of anaemia. Assessment of vital signs and the acuity of the anaemia is the single most important step in ensuring safety for the patient.

Regenerative anaemias should always actively engage the clinician because of their propensity for rapid deterioration, and almost all children with these anaemias need immediate management in a hospital setting. Children with aregenerative anaemias can often be managed in the outpatient setting, with the exception of those with severe anaemia or megaloblastic anaemia.

Iron deficiency anaemia is the most common anaemia encountered in clinical practice, and severe anaemia can develop slowly with minimal symptoms. Although seemingly straightforward, the dietary and behavioural management of children with iron deficiency anaemia, especially the toddler age group, requires substantial time and effort on behalf of the clinician if the parents are to be adequately supported for a successful outcome. In this context, investigations can be kept to a minimum but adequate follow up is essential. Rarer causes of anaemia usually require specialist management. MT

Further reading

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