New guidelines

Hereditary spherocytosis; new guidelines

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Hereditary spherocytosis

Hereditary spherocytosis (HS) is the commonest cause of haemolysis in northern Europe. Most children have mild disease with little interference with lifestyle. Presentation with parvovirus B19 infection causing transient severe anaemia is not uncommon. The laboratory diagnosis of HS is usually straightforward and additional tests are rarely required. A new test, EMA binding, will probably replace the time consuming and non-specific osmotic fragility test. Splenectomy leads to improved red cell survival and is indicated for severe and probably moderate disease; gallstones may occur in the first decade, and if symptomatic are an indication for both cholecystectomy and splenectomy. Splenectomy is associated with a life long increased risk of sepsis, which has not been completely eradicated by preoperative vaccinations and post-splenectomy antibiotic prophylaxis.

Haemolysis is an uncommon cause of anaemia in children. The commonest cause of anaemia is iron deficiency, globally a major problem; worldwide, haemolysis is most commonly associated with a red cell enzyme deficiency, glucose-6-dehydrogenase deficiency (G6PD). Haemolysis produced by G6PD deficiency is usually episodic and self-limiting; in contrast the haemolysis associated with hereditary spherocytosis, a red cell membrane disorder, is chronic, and prone to exacerbations with intercurrent infections. Hereditary spherocytosis (HS) is the commonest cause of inherited haemolysis in northern Europe and the USA; the incidence is in the order of 1 in 5000 births, but rises to 1 in 2000 if milder forms are considered.[1] It has been reported in most ethnic groups, and can come to light at any age, mild cases often being diagnosed in adulthood. Although HS is relatively common, there has been little published advice concerning management; new guidelines have been produced[2] and this article summarises some of the relevant issues.

PATHOLOGY

The defects in hereditary spherocytosis lie in the red cell membrane (fig 1).[2] The proteins essential for the integrity of the membrane structure lie immediately under the lipid bilayer; horizontal alpha and beta spectrin molecules form heterodimers with linkage to vertical elements—ankyrin, proteins 4.1 and 4.2, and band 3 (which is a transmembrane protein). Different genes code each of these proteins, thus hereditary spherocytosis is a heterogeneous disorder, which can result from a defect in any one of these proteins. The resultant destabilisation of the membrane leads to both abnormal morphology and a reduced red cell life span (from the normal 120 to a few days). The shorter the red cell life span, the worse the clinical effects. The defect, and therefore the clinical severity, tends to be fairly constant within a given family, but between families varies from mild asymptomatic haemolysis to severe continuous anaemia with jaundice. Inheritance is usually dominant (75%).

CLINICAL FEATURES

The classical clinical features of haemolysis (whatever the cause) are anaemia, jaundice, and splenomegaly. However, anaemia is often mild or absent when the haemolysis is well compensated (about a third of cases), as the bone marrow is able to increase red cell output some 6 to 8-fold; the only finding in some affected individuals is a raised reticulocyte count reflecting the increased marrow turnover. Jaundice is variable, often absent, and likely to increase when the marrow is stressed by intercurrent infection. Splenomegaly is usual, being generally mild, and a finding of massive splenomegaly should prompt a search for an alternative diagnosis. The enlarged spleen is not more prone to rupture than in a normal person, and the size is neither an indication for splenectomy nor for any restriction of activity.

Hereditary spherocytosis can present at any age from the neonatal period to the ninth decade, depending on severity. In the neonatal period jaundice is common, occasionally requiring exchange transfusion. It is important that affected families are aware of this. The severity of the jaundice (which may develop over several days) does not necessarily predict a severe subsequent course, and is perhaps not dependent on the severity of the membrane defect alone.

Children with hereditary spherocytosis may be usefully classified by clinical features as ''severe'', ''moderate'', or ''mild'' using the criteria shown in table 1.[3] This assessment should be made when the child is in a stable baseline state, as with intercurrent illness the severity may be overestimated. Children with severe hereditary spherocytosis (rare, about 5%) are constantly anaemic, and may be transfusion dependent, especially in the first few years of life. Treatment with erythropoietin may be beneficial and reduce transfusion requirements in the first year of life.[4 5] After this time, regular transfusion is rarely required; most children can tolerate a low haemoglobin level and this alone should not be a transfusion trigger. Severe HS is the exception rather than the rule; most children with HS have a normal or only slightly reduced haemoglobin and lead a

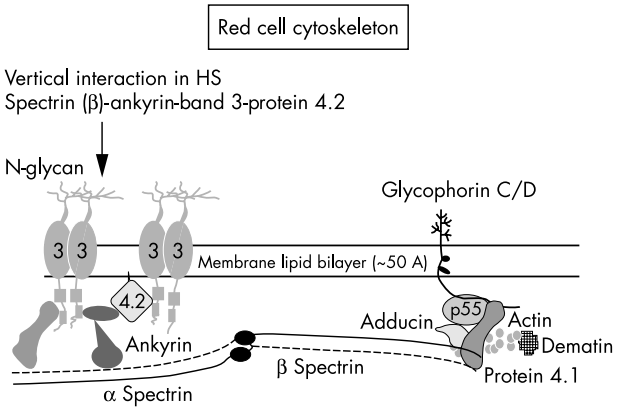

Figure 1 Schematic presentation of the structural organisation of red cell cytoskeleton. β Spectrin is the key component in that it pairs with α spectrin to form a heterodimer, and it has binding sites for ankyrin and protein 4.1. The common protein defects are associated with spectrin (α and/or β), ankyrin, band 3 protein, and protein 4.1.

normal life. Haemolysis is associated with increased red cell turnover and an increased pigment load for the liver – this may result in gallstones developing as early as the first or second decade of life, and the risk is increased with co-inheritance of Gilbert syndrome.[6] Generally, the higher the reticulocyte count, the higher the risk of developing gallstones. This is therefore one of the parameters which may guide a decision for splenectomy.

People with HS (both children and adults) may remain undiagnosed for years or decades if haemolysis is mild. In both childhood and adulthood, parvovirus infection is an important initial presentation. Parvovirus B19 leads to red cell aplasia for a few days. In people with a normal red cell life span this is barely noticeable, but in people with HS or any other form of haemolytic anaemia, parvovirus infection leads to a sudden profound fall in haemoglobin level to as low as 20 or 30 g/l.[7] Such individuals often feel unwell, and may have an associated mild leucopenia and thrombocytopenia leading to fear of a more sinister diagnosis. The diagnosis may be suspected from the blood film (spherocytes) and the clinical finding of splenomegaly. The reticulocyte count is characteristically low at the onset, but will increase rapidly in the recovery period. Once recovered from the infection (within a week or two), parvovirus B19 infection does not recur; it is then important to establish the usual baseline haemoglobin and reticulocyte count as often people who present in this way have otherwise mild disease. An increase in haemolysis (and therefore a drop in haemoglobin) may be produced by stress or other infections, but such severe anaemia due to aplasia is unlikely to recur; no other infection produces such a profound fall in the haemoglobin. Helpful pointers to the diagnosis of HS include a family history of others with similar ''aplastic'' crises, jaundice, or splenectomy. It is surprising that people who have had a splenectomy in the past may not know that the reason was an abnormality in the red blood cells. People with known HS who have not had parvovirus infection, and their family doctors, should be warned of possible future infection, as the degree of anaemia and symptoms can be alarming. Transfusion support may be required (usually a single transfusion episode). It is helpful to confirm the diagnosis by showing an increasing IgM parvovirus antibody titre or demonstration of parvovirus DNA in the blood. At present there is no way of preventing infection, but a novel recombinant parvovirus vaccine has successfully shown seroconversion in adults in a phase 1 trial.[8] Parvovirus infection is readily spread so that several members of a family may be infected at the same time.[9]

People with mild HS may remain undiagnosed for decades and only be discovered when spherocytes are seen when a blood count is done for another indication, or the person is found incidentally to have an enlarged spleen. Some individuals will be diagnosed in pregnancy as a result of routine blood counts.

LABORATORY DIAGNOSIS

The key features are spherocytes on the blood film and a raised reticulocyte count with or without anaemia. The bilirubin level (unconjugated) is often raised. The red cells may show a reduced red cell volume (MCV) and increased red cell haemoglobin concentration (MCHC). The differential diagnosis is from autoimmune haemolytic anaemia (AIHA); a direct antiglobulin test (for the detection of antibodies on the red cells) will be negative in HS and usually positive in AIHA. The clinical context is important. People with HS are usually clinically well and often have a positive family history; AIHA is rare in children and most commonly associated with an acute viral infection. With the classical clinical picture and these simple laboratory tests, there is usually no need for further investigation. The osmotic fragility test (OF) is time consuming, labour intensive, and adds nothing to the diagnosis if there are obvious spherocytes on the film. The OF does not distinguish between the causes of spherocytosis and so will be positive in AIHA. It can also be falsely negative in the presence of iron deficiency and obstructive jaundice, and is difficult to interpret in neonates who have a different normal range. (Normal neonates may have spherocytes and it may not be possible to confirm a diagnosis of HS for some months.) Confirmatory tests for HS are rarely required. A particularly promising test, now being introduced in many laboratories, is the eosin-5-maleimide (EMA) binding test performed by flow cytometry.[11 12] EMA binds to band 3, a skeletal protein, and the test has a high sensitivity (92.7%) and specificity (99.1%) for HS. The test can be performed rapidly (within two hours) on a small sample of blood.

Although it may be possible to identify the genetic basis of the HS in any given family (that is, to see which protein is defective), this is usually unnecessary for clinical management. Genetic analysis is a research investigation, and is only helpful in very unusual cases. The majority of individuals with HS are easily diagnosed with routine methods, providing the laboratory staff are given the appropriate clinical information. Doubt may occasionally arise in the context of an atypical appearance of the blood film; there are some important and rare disorders of red cells that can resemble HS. Atypical cases must therefore be carefully reviewed with the haematologist. In these cases, further investigation may be necessary.[2]

CLINICAL MANAGEMENT

Once the diagnosis is made, it is important to reassure parents and children that HS is not generally a serious disorder, and no restrictions are required on activity or lifestyle. If a child has been diagnosed as a result of parvovirus infection, both parents and medical staff may have a false impression of the severity, so it is important to review the blood count some months later to obtain a more accurate reflection of the normal status. Family studies will be appropriate. There may be adults in the family who have had splenectomy in the past for HS. This raises other issues; in the past splenectomy was performed more readily than it is now (see below) and adults may not be aware of their long term infection risks. Splenectomy in other family members does not necessarily predict for the newly diagnosed child because criteria for surgery are now stricter.

Children with severe HS may have significant anaemia (for example, Hb 60 g/l) but are usually remarkably well and active. Transfusion is rarely required and should not be based on the haemoglobin level alone. In general, once the diagnosis and baseline severity of HS in a child are established, it is not necessary to perform repeated blood tests unless there is an additional clinical indication (such as intercurrent infection and pallor, or an increase in

Table 1 Classification of hereditary spherocytosis (modified from Eber *et al*[3])

Classification	Mild	Moderate	Severe
Haemoglobin (g/l)	110–150	80–120	60–80
Reticulocyte count (%)	3–6	>6	>10
Bilirubin (μg/l)	17–34	>34	>51
Splenectomy	Usually not required	Indicated during school age, usually before puberty	Necessary—delay until 6 years if possible

jaundice). A routine annual review is usually sufficient together with an open door policy for potential complications such as parvovirus infection, or abdominal pain, which may trigger investigation for gallstones.

It is traditional for children with chronic haemolysis to receive oral folate supplements, but most children in developed countries consume well above the minimum daily requirement. There is no strong evidence to support universal folate supplementation in HS, and it is likely that it is only required in children with severe and moderate HS, but for all patients during pregnancy. There is no standardised regimen; a reasonable daily dose is 2.5 mg up to the age of 5 years and 5 mg daily thereafter.

SPLENECTOMY

The most important question in the management of HS is to decide whether splenectomy is likely to be of benefit, and when it should be carried out. Once it was recognised that splenectomy abrogated the clinical symptoms of HS, it was universally applied; however, this was followed by the recognition of the risk of severe overwhelming post-splenectomy sepsis, often fatal,[13 14] usually caused by pneumococcal species. The risk is age related, being highest in the youngest children and within the first few years after surgery. Current UK guidelines recommend pre-splenectomy vaccination against pneumococcus, haemophilus, and meningococcus, together with long term (lifelong) postoperative penicillin prophylaxis.[15 16] These measures do not completely eliminate the risk.[17 18] There remain many unanswered questions: How long does pneumococcal immunity last? Which is the best vaccine? How long should penicillin prophylaxis be continued? The increased susceptibility to serious pneumococcal sepsis is lifelong,[19] but there are no trials showing benefit of long term antibiotics, and other guidelines are more cautious, recommending penicillin prophylaxis for at least two years in adults, and at least five years in children,[20] rather than lifelong. This is partly an acknowledgement of the increase in penicillin resistant pneumococci.[21] The decision for splenectomy needs to be carefully made, weighing up advantages against the small but real risks, which must be carefully discussed with the child and family. Chronic anaemia is debilitating; although the young child tolerates significant chronic anaemia well in terms of activity, rarely it can lead to increased cardiac output with cardiomegaly, and leg ulcers. Children with chronic anaemia may show a fall-off in growth rate and weight gain as they approach puberty. Chronic severe haemolysis is associated with a significant risk of gallstones, which may become symptomatic as early as the first or second decade of life. Since the spleen is the site of destruction of the abnormal red cells, splenectomy produces a significant increase in the red cell life span to normal or near normal in most cases. The red cell morphology does not improve, but red cell destruction is reduced, leading to improvement in the haemoglobin level, and reduction of the reticulocyte count. The increased risk of gallstone development is also corrected.[22] There are therefore significant advantages in proceeding to splenectomy in children with severe HS, and probably most with moderate HS. Splenectomy should be avoided if possible in the young child, and if possible, postponed until the child is at least 6 years of age. Some centres advocate partial splenectomy for the most severe transfusion dependent children; this ameliorates the haemolysis, but experience with this technique is limited to a few centres, and many of these children subsequently require repeat surgery to complete splenectomy.[23 24]

It is often convenient to perform splenectomy before the child moves into secondary education; the decision for elective surgery can be made over a period of time and it may be helpful for children and parents to talk to other families who have experience. Parents find it particularly difficult to decide for elective surgery when a child seems very well, particularly in the face of some risks. However, the child or young adult often reports a considerable improvement in wellbeing after surgery. Traditionally, surgery has been open, laparotomy, but there is increasing experience in many centres with laparoscopic surgery, which has the advantage of more rapid recovery, a shorter hospital stay, and a better cosmetic result. The decision must rest with the surgeon, and is dependent on experience and availability of suitable equipment.

When a child has had symptoms of gall bladder disease, most surgeons would remove the gall bladder at the time of splenectomy; conversely, if a child requires surgery for gall bladder disease complicating HS, the spleen should be removed at the same time.[2]

It is reasonable to perform ultrasound examination of the gall bladder towards the end of the first decade, as the finding of gall stones, even without symptoms at this age may influence the decision for splenectomy. A recent review describes 44 patients aged between 1 and 22 years who underwent annual ultrasound examination from the age of 4 years or at the time of diagnosis.[25] Overall 18 (41%) developed gallstones, with a higher incidence in those with moderate and severe HS; however, stones developed in 4/14 (29%) with mild HS at a median age of 13 years, and overall 94% of stones developed by this age. Five patients had symptoms suggestive of cholelithiasis prior to detection by ultrasound.

It should be noted that it is usual for the platelet count to rise post-splenectomy, sometimes to levels higher than 1000×10^9/l, but there is no evidence that this on its own is a risk factor for thrombosis in people with HS in the short or long term, and in this context, high platelet counts do not need any treatment. People with some forms of hereditary stomatocytosis have an increased risk of thrombosis after splenectomy;[26] this emphasises the importance of careful evaluation of cases with atypical red cell morphology by a haematologist.

CONCLUSION

HS is the commonest form of haemolytic anaemia seen in northern Europe. Most children have mild disease, can live a normal life, and do not require splenectomy. Parvovirus B19 infection can cause an acute aplastic phase, but does not recur. Splenectomy is reserved for those with severe disease or who develop symptomatic gallstones, when cholecystectomy should be performed at the same time. The lifelong risk of post-splenectomy sepsis must be discussed fully with the family, and adequate prophylaxis undertaken.

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IMAGES IN PAEDIATRICS

BCG lymphadenitis

A 3 month old, otherwise well baby of Chinese origin, who had received BCG vaccine in the left deltoid region on the second day of life, presented with a one month history of a lump in the left axilla (see fig). Examination revealed a fluctuant mass (5×8 cm) at the left anterior axillary fold. Ultrasonography confirmed enlarged but non-suppurative lymph nodes. A presumptive diagnosis of BCG lymphadenitis was made and treatment was started with isoniazid. A month later the swelling increased in size and became more fluctuant. Surgical incision and drainage was performed, which revealed caseous material characteristic of tuberculous infection.

Isoniazid was continued for a total of three months and the lesion healed uneventfully.

On a prolonged culture, Bacille Calmette-Guerin was grown that was resistant to isoniazid but sensitive to ciprofloxacin, ethambutol, and rifampicin.

Although BCG lymphadenitis is a well recognised condition, it is not commonly seen in UK district general hospitals. Treatment of BCG lymphadenitis remains controversial. In one series,[1] surgery was proposed as the most effective treatment in advanced cases with no reported recurrence or fistula formation. Goraya and Virdi,[2] however, suggested that no treatment was required in non-suppurative lymphadenitis. In the case of suppuration, surgical treatment either by needle aspiration or surgical excision could be undertaken. In our case, treatment with isoniazid was probably non-contributory.

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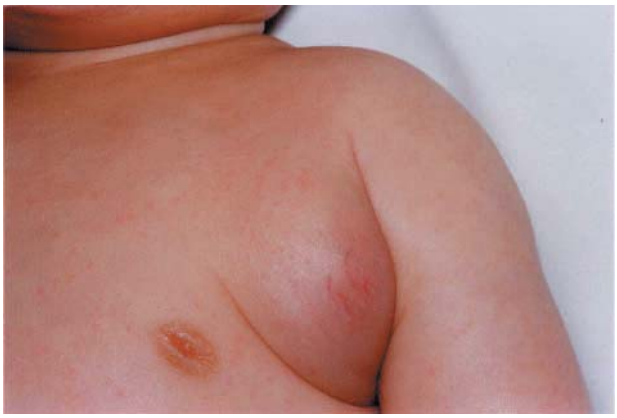

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Dr Mohammed Al Moudaris died after a short illness on 15th April 2004. For 13 years he had been a general paediatrician with a special interest in allergy at the Hospital of St. Cross, Rugby and Walsgrave Hospital, Coventry. He was a very popular member of staff and will be sadly missed by patients and colleagues. He leaves a wife, Nudhar Hadid (a consultant radiologist with the same Trust), a daughter, May (an architect), and a son, Al, who graduated as a doctor this summer.