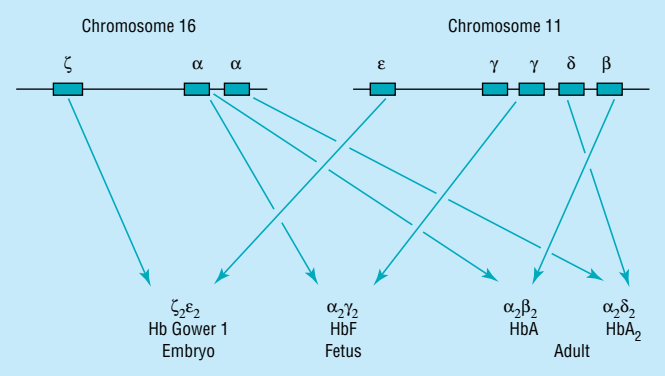
ABC of clinical haematology
The hereditary anaemias

David J Weatherall

Hereditary anaemias include disorders of the structure or synthesis of haemoglobin; deficiencies of enzymes that provide the red cell with energy or protect it from chemical damage; and abnormalities of the proteins of the red cell's membrane. Inherited diseases of haemoglobin, haemoglobinopathies, are by far the most important.

The structure of human haemoglobin (Hb) changes during development. By the 12th week embryonic haemoglobin is replaced by fetal haemoglobin (Hb F), which is slowly replaced after birth by the adult haemoglobins, Hb A and Hb A_2. Each type of haemoglobin consists of two different pairs of peptide chains; Hb A has the structure $\alpha_2\beta_2$ (namely, two α chains plus two β chains), Hb A_2 has $\alpha_2\delta_2$, and Hb F has $\alpha_2\gamma_2$.

The haemoglobinopathies consist of structural haemoglobin variants (the most important of which are the sickling disorders) and thalassaemias (hereditary defects of the synthesis of either the α or β globin chains).



Simplified representation of the genetic control of human haemoglobin. Because α chains are shared by both fetal and adult haemoglobin, mutations of the α globin genes affect haemoglobin production in both fetal and adult life; diseases that are due to defective β globin production are only manifest after birth when Hb A replaces Hb F.

The sickling disorders

Classification and inheritance

The common sickling disorders consist of the homozygous state for the sickle cell gene—that is, sickle cell anaemia (Hb SS)—and the compound heterozygous state for the sickle cell gene and that for either Hb C (another β chain variant) or β thalassaemia (termed Hb SC disease or sickle cell β thalassaemia). The sickle cell mutation results in a single amino acid substitution in the β globin chain; heterozygotes have one normal (β^A) and one affected β chain (β^S) gene and produce about 60% Hb A and 40% Hb S; homozygotes produce mainly Hb S with small amounts of Hb F. Compound heterozygotes for Hb S and Hb C produce almost equal amounts of each variant, whereas those who inherit the sickle cell gene from one parent and β thalassaemia from the other make predominantly sickle haemoglobin.

Sickling syndromes
- Hb SS (sickle cell anaemia)
- Hb SC
- Hb S/β^+ thalassaemia
- Hb S/β^o thalassaemia
- Hb SD

Pathophysiology

The amino acid substitution in the β globin chain causes red cell sickling during deoxygenation, leading to increased rigidity and aggregation in the microcirculation. These changes are reflected by a haemolytic anaemia and episodes of tissue infarction.

Sickle cell trait (Hb A and Hb S)
- Less than half the Hb in each red cell is Hb S
- Occasional renal papillary necrosis
- Inability to concentrate the urine (older individuals)
- Red cells do not sickle unless oxygen saturations $<40\%$ (rarely reached in venous blood)
- Painful crises and splenic infarction have been reported in severe hypoxia—such as unpressurised aircraft, anaesthesia

Sickling is more common where Hb S is present with another β globin chain abnormality—such as Hb S and Hb C (Hb SC) or Hb S and Hb D (Hb SD)

Geographical distribution

The sickle cell gene is spread widely throughout Africa and in countries with African immigrant populations; some Mediterranean countries; the Middle East; and parts of India. Screening should not be restricted to people of African origin.

Clinical features

Sickle cell carriers are not anaemic and have no clinical abnormalities. Patients with sickle cell anaemia have a haemolytic anaemia, with haemoglobin concentration 60-100 g/l and a high reticulocyte count; the blood film shows polychromasia and sickled erythrocytes.

Patients adapt well to their anaemia, and it is the vascular occlusive or sequestration episodes ("crises") that pose the main threat.

Sickle cell anaemia (homozygous Hb S)
- Anaemia (Hb 60-80 g/l)—Symptoms milder than expected as Hb S has reduced oxygen affinity (that is, gives up oxygen to tissues more easily)
- Sickled cells may be present in blood film—Sickling occurs at oxygen tensions found in venous blood; cyclical sickling episodes
- Reticulocytes—Raised to 10-20%
- Red cells contain $\geq 80\%$ Hb S (rest is mainly fetal Hb)
- Variable haemolysis
- Hand and foot syndrome (dactylitis)

Adult
- Intermittent episodes, or crises, characterised by bone pain, worsening anaemia, or pulmonary or neurological disease
- Chronic leg ulcers
- Gall stones

Complications of sickle cell disease

- Hand and foot syndrome—Seen in infancy; painful swelling of digits
- Painful crises—Later in life; generalised bone pain; precipitated by cold, dehydration but often no cause found; self limiting over a few days
- Aplastic crisis—Marrow temporarily hypoplastic; may follow parvovirus infection; profound anaemia; reduced reticulocyte count
- Splenic sequestration crisis—Common in infancy; progressive anaemia; enlargement of spleen
- Hepatic sequestration crisis—Similar to splenic crisis but with sequestration of red cells in liver
- Lung or brain syndromes—Sickling of red cells in pulmonary or cerebral circulation
- Infections—Particularly *Streptococcus pneumoniae* and *Haemophilus influenzae*
- Gall stones
- Progressive renal failure
- Chronic leg ulcers
- Recurrent priapism
- Aseptic necrosis of humoral/femoral head
- Chronic osteomyelitis—Sometimes due to *Salmonella typhi*

Diagnosis

Sickle cell anaemia should be suspected in any patient of an appropriate racial group with a haemolytic anaemia. It can be confirmed by a sickle cell test, although this does not distinguish between heterozygotes and homozygotes. A definitive diagnosis requires haemoglobin electrophoresis and the demonstration of the sickle cell trait in both parents.

Prevention and treatment

Pregnant women in at-risk racial groups should be screened in early pregnancy and, if the woman and her partner are carriers, should be offered either prenatal or neonatal diagnosis. As soon as the diagnosis is established babies should receive penicillin daily and be immunised against *Streptococcus pneumoniae*, *Haemophilus influenzae* type b and *Neisseria meningitidis*. Parents should be warned to seek medical advice on any suspicion of infection.

Sickling variants

Hb SC disease is characterised by a mild anaemia and fewer crises. Important microvascular complications, however, include retinal damage and blindness, aseptic necrosis of the femoral heads, and recurrent haematuria. The disease is occasionally complicated by pulmonary embolic disease, particularly during and after pregnancy; these episodes should be treated by immediate exchange transfusion. Patients with Hb SC should have annual ophthalmological surveillance; the retinal vessel proliferation can be controlled with laser treatment. The management of the symptomatic forms of sickle cell β thalassaemia is similar to that of sickle cell anaemia.

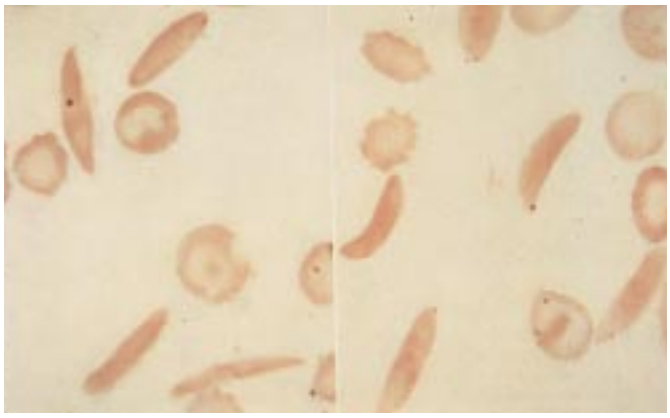
The thalassaemias

Classification

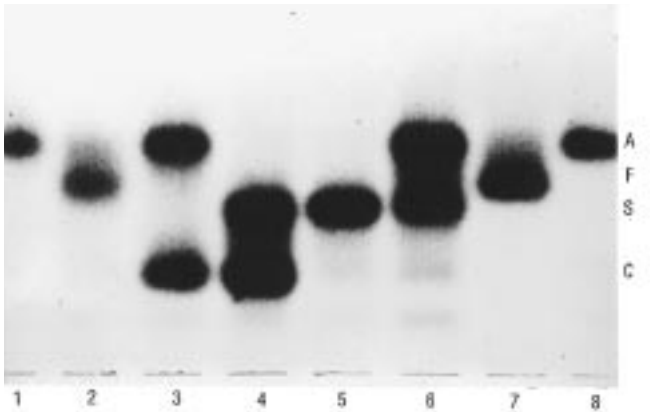
The thalassaemias are classified as α or β thalassaemias, depending on which pair of globin chains is synthesised inefficiently. Rarer forms affect both β and δ chain production, δβ thalassaemias.

Distribution

The disease is broadly distributed throughout parts of Africa, the Mediterranean region, the Middle East, the Indian subcontinent, and South East Asia and occurs sporadically in all racial groups. Like sickle cell anaemia, it is thought to be common because carriers have been protected against malaria.



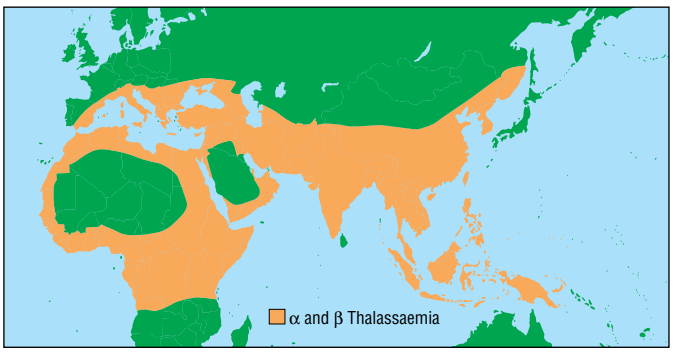
Peripheral blood film from patient with sickle cell anaemia showing sickled erythrocytes.



Haemoglobin electrophoresis showing (1) normal, (2) newborn, (3) Hb C trait (A-C), (4) Hb SC disease (SC), (5) sickle cell disease (SS), (6) sickle cell trait (A-S), (7) newborn, (8) normal.

Treatment of major complications of sickle cell disease

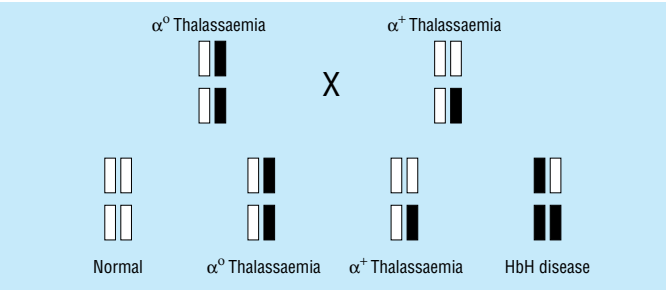
- *Hand and foot syndrome*—Hydration; paracetamol
- *Painful crises*—Hydration; analgesia (including graded intravenous analgesics); oxygen (check arterial blood gases); blood cultures; antibiotics
- *Pulmonary infiltrates*—Especially with deterioration in arterial gases, falling platelet count and/or haemoglobin concentration suggesting lung syndrome requires urgent exchange blood transfusion to reduce Hb S level
- *Splenic sequestration crisis*—Transfusion; splenectomy to prevent recurrence
- *Neurological symptoms*—Immediate exchange transfusion followed by long term transfusion
- *Prevention of crises*—Ongoing trials of cytotoxic agent hydroxyurea show that it raises Hb F level and ameliorates frequency and severity of crises; long term effects unknown



Distribution of the thalassaemias (orange area).

Inheritance

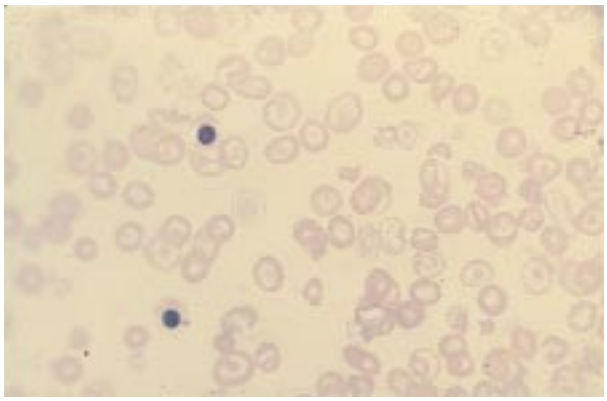
The β thalassaemias result from over 150 different mutations of the β globin genes, which reduce the output of β globin chains, either completely (β^0 thalassaemia) or partially (β^+ thalassaemia). They are inherited like sickle cell anaemia; carrier parents have a one in four chance of having a homozygous child. The genetics of the α thalassaemias is more complicated because normal people have two α globin genes on each of their chromosomes 16. If both are lost (α^0 thalassaemia) no α globin chains are made, whereas if only one of the pair is lost (α^+ thalassaemia) the output of α globin chains is reduced. Impaired α globin production leads to excess γ or β chains that form unstable and physiologically useless tetramers, γ_4 (Hb Bart's) and β_4 (Hb H). The homozygous state for α^0 thalassaemia results in the Hb Bart's hydrops syndrome, whereas the inheritance of α^0 and α^+ thalassaemia produces Hb H disease.



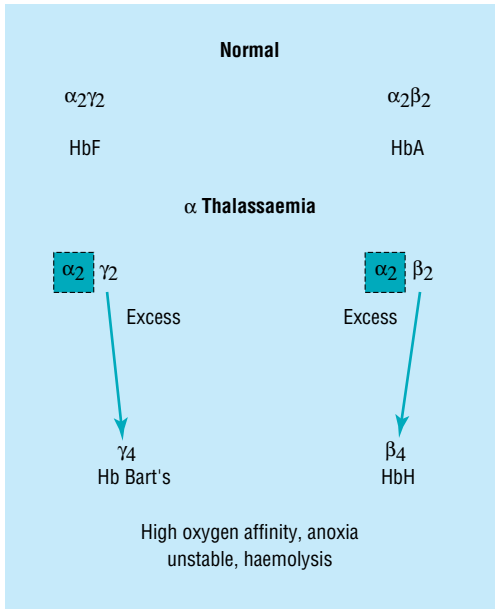
Inheritance of Hb H disease (open boxes represent normal α globin genes and black boxes deleted α globin genes).

The β thalassaemias

Heterozygotes for β thalassaemia are asymptomatic, have hypochromic microcytic red cells with a low mean corpuscular haemoglobin and mean cell volume, and have an Hb A_2 level of about twice normal. Homozygotes, or those who have inherited a different β thalassaemia gene from both parents, usually develop severe anaemia in the first year of life. This results from a deficiency of β globin chains; excess α chains precipitate in the red cell precursors leading to their damage, either in the bone marrow or the peripheral blood. Hypertrophy of the ineffective bone marrow leads to skeletal changes, and there is variable hepatosplenomegaly. The Hb F level is always raised. If these children are transfused, the marrow is "switched off," and growth and development may be normal. However, they accumulate iron and may die later from damage to the myocardium, pancreas, or liver. They are also prone to infection and folic acid deficiency. Milder forms of β thalassaemia (thalassaemia intermedia), although not transfusion dependent, are sometimes associated with similar bone changes, anaemia, leg ulcers, and delayed development.



Peripheral blood film in homozygous β thalassaemia showing pronounced hypochromia and anisocytosis with nucleated red blood cells.



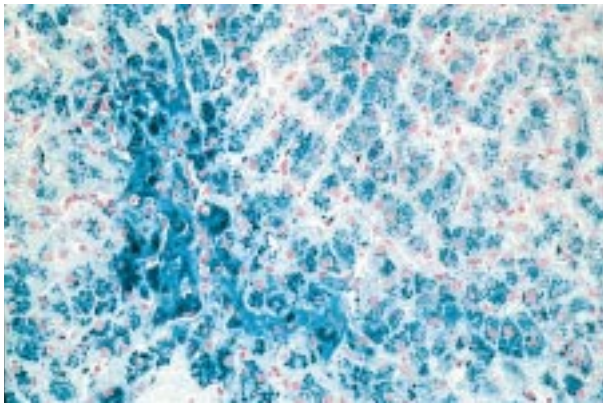
Pathophysiology of α thalassaemia.

β Thalassaemia trait (heterozygous carrier)

- Mild hypochromic microcytic anaemia
  - Haemoglobin 90-110 g/l
  - Mean cell volume 50-70 fl
  - Mean corpuscular haemoglobin 20–22 pg
- No clinical features, patients asymptomatic
- Often diagnosed on routine blood count
- Raised Hb A_2 level

β Thalassaemia major (homozygous β thalassaemia)

- Severe anaemia
- Blood film
  - Pronounced variation in red cell size and shape
  - Pale (hypochromic) red cells
  - Target cells
  - Basophilic stippling
  - Nucleated red cells
  - Moderately raised reticulocyte count
- Infants are well at birth but develop anaemia in first few months of life when switch occurs from γ to β globin chains
- Failure to thrive, etc



Liver biopsy from patient with β thalassaemia showing pronounced iron accumulation.

The α thalassaemias

The Hb Bart's hydrops fetalis syndrome is characterised by the stillbirth of a severely oedematous (hydropic) fetus in the second half of pregnancy. Hb H disease is associated with a moderately severe haemolytic anaemia. The carrier states for α^o thalassaemia or the homozygous state for α^+ thalassaemia result in a mild hypochromic anaemia with normal Hb A_2 levels. They can only be distinguished with certainty by DNA analysis in a specialised laboratory. In addition to the distribution mentioned above, α thalassaemia is also seen in European populations in association with mental retardation; the molecular pathology is quite different to the common inherited forms of the condition.

Prevention and treatment

As β thalassaemia is easily identified in heterozygotes, pregnant women of appropriate racial groups should be screened; if a woman is found to be a carrier, her partner should be tested and the couple counselled. Prenatal diagnosis by chorionic villus sampling can be carried out between the 9th and 13th weeks of pregnancy. If diagnosis is established, the patients should be treated by regular blood transfusion with surveillance for hepatitis C and related infections.

To prevent iron overload, overnight infusions of desferrioxamine together with vitamin C should be started, and the patient's serum ferritin and hepatic iron concentrations should be monitored; complications of desferrioxamine include infections with *Yersinia* spp, retinal and acoustic nerve damage, and reduction in growth associated with calcification of the vertebral discs. The place of the oral chelating agent deferiprone (L1) is still under evaluation; though effective, it may cause neutropenia and transient arthritis. Bone marrow transplantation—if appropriate HLA-DR matched siblings are available—may carry a good prognosis if carried out early in life. Treatment with agents designed to raise the production of Hb F is still at the experimental stage.

In β thalassaemia and Hb H disease progressive splenomegaly or increasing blood requirements, or both, indicate that splenectomy may be beneficial. Patients who undergo splenectomy should be vaccinated against *S pneumoniae*, *H influenzae*, and *N meningitidis* preoperatively and should receive a maintenance dose of oral penicillin indefinitely.

The α thalassaemias

- α/ α α 1 α gene deleted
- Asymptomatic
- Minority show reduced mean cell volume and mean corpuscular haemoglobin

- α/ - α or α α/ - - 2 α genes deleted
- Haemoglobin is normal or slightly reduced
- Reduced mean cell volume and mean corpuscular haemoglobin
- No symptoms

- -/ - α 3 α genes deleted, Hb H disease
- Chronic haemolytic anaemia
- Reduced α chain production with formation of β_4 tetramers (β_4 is termed Hb H)
- Hb H is unstable and precipitates in older red cells
- Haemoglobin is 70-110 g/l, though may be lower
- Reduced mean cell volume and mean corpuscular haemoglobin
- Clinical features: jaundice, hepatosplenomegaly, leg ulcers, gall stones, folate deficiency

- -/ - - 4 α genes deleted, Hb Bart's hydrops
- No α chains produced
- Mainly γ, forms tetramers (γ_4 = Hb Bart's)
- Intrauterine death or stillborn at 25–40 weeks or dies soon after birth

α α/ α α Represents 2 α globin genes inherited from each parent
Changes due to α thalassaemia are present from birth unlike in β thalassaemia

Women with thalassaemia
- Women with the haematological features of thalassaemia trait with normal Hb A_2 levels should be referred to a centre able to identify the different forms of α thalassaemia
- Those with α^o thalassaemia trait—if their partners are similarly affected—should be referred for prenatal diagnosis
- This is because the haemoglobin Bart's hydrops syndrome is associated with an increased risk of toxaemia of pregnancy and postpartum bleeding due to a hypertrophied placenta

Red cell enzyme defects

Red cells have two main metabolic pathways, one burning glucose anaerobically to produce energy, the other generating reduced glutathione to protect against injurious oxidants. Many inherited enzyme defects have been described. Some of those of the energy pathway—for example, pyruvate kinase deficiency—cause haemolytic anaemia; any child with this kind of anaemia from birth should be referred to a centre capable of analysing the major red cell enzymes.

Glucose-6-phosphate dehydrogenase deficiency (G6PD) involves the protective pathway. It affects millions of people worldwide, mainly the same racial groups as are affected by the thalassaemias. Glucose-6-phosphate dehydrogenase deficiency is sex linked and affects males predominantly. It causes neonatal jaundice, sensitivity to fava beans (broad beans), and haemolytic responses to oxidant drugs.

Drugs causing haemolysis patients with in G6PD deficiency

Antimalarials
Primiquine
Pamaquine
*Analgesics**
Phenacetin
Acetyl salicylic acid
Others
Sulphonamides
Nalidixic acid
Dapsone

*Probably only at high doses

Red cell membrane defects

The red cell membrane is a complex sandwich of proteins that are required to maintain the integrity of the cell. There are many inherited defects of the membrane proteins, some of which cause haemolytic anaemia. Hereditary spherocytosis is due to a structural change that makes the cells more leaky. It is particularly important to identify this disease because it can be "cured" by splenectomy.

There are many rare inherited varieties of elliptical or oval red cells, some associated with chronic haemolysis and response to splenectomy. A child with a chronic haemolytic anaemia with abnormally shaped red cells should always be referred for expert advice.

Other hereditary anaemias

Other anaemias with an important inherited component include Fanconi's anaemia (hypoplastic anaemia with skeletal deformities), Blackfan-Diamond anaemia (red cell aplasia), and several forms of congenital dyserythropoietic anaemia.

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The ABC of Clinical Haematology is edited by Drew Provan, consultant haematologist and honorary senior lecturer at the Southampton University Hospitals NHS Trust, and Andrew Henson, clinical research fellow, university department of primary care, Royal South Hants Hospital, Southampton.

Lesson of the week

Are spontaneous hypoglycaemia, raised plasma insulin and C peptide concentrations, and abnormal pancreatic images enough to diagnose insulinoma?

P Perros, A K Henderson, D C Carter, A D Toft

Sulphonylurea misuse should be excluded before undertaking an exploratory laparotomy for insulinoma

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Spontaneous fasting hypoglycaemia is rare, and in adults the usual underlying cause is insulinoma.[1] Most insulinomas are small tumours, and currently available imaging techniques fail to detect a large proportion of them, so that the diagnosis may have to be based on the presence of spontaneous hypoglycaemia associated with inappropriately raised plasma insulin and C peptide concentrations. In such cases laparotomy with exploration of the pancreas may be the next logical step.

Case report

A 42 year old nurse presented with a five month history of dizziness, ataxia, and paraesthesiae, which improved after eating carbohydrates. Her medical history included acute sarcoidosis, which had resolved 24 years ago, temporal lobe epilepsy diagnosed 13 years previously, and episodic numbness of her right shoulder and face for 12 years, the cause of which had been attributed to possible demyelination. She took sodium valproate to control her epilepsy. She did not smoke and drank minimal quantities of alcohol.

Clinical examination did not indicate any abnormality. During a supervised 24 hour fast in hospital she remained symptom free with normal glucose concentrations. Four months later her symptoms became more frequent and severe. On several occasions her plasma glucose concentration was in the hypoglycaemic range (1.7-2.2 mmol/l) and accompanied by symptoms: these resolved with the administration of oral carbohydrate. Plasma insulin and C peptide concentrations during hypoglycaemia were raised at 170 mU/l (fasting reference range undetectable to 13 mU/l) and 7.2 nmol/l (reference range 0.3-1.12 nmol/l), respectively. She was given a provisional diagnosis of insulinoma and referred for surgical assessment and treatment.

During her admission to the surgical ward she required continuous intravenous dextrose to prevent hypoglycaemia. A computed tomogram of her abdomen showed a faint blush after contrast medium in the body of the pancreas. Coeliac axis angiography showed a possible lesion in the body of the pancreas of doubtful clinical relevance. At laparotomy no pancreatic tumour could be identified after full mobilisation of the pancreas, bimanual palpation, and intraoperative ultrasonography. The abdomen was closed without further surgical intervention. Her hypoglycaemia recurred five days postoperatively. She was discharged on a regimen of diazoxide, with a view to subsequent reassessment and the possibility of hepatic portal vein sampling to locate the source of excessive insulin production.

A stored plasma sample taken during an episode of hypoglycaemia while she had been an inpatient was subsequently submitted for sulphonylurea assay. This showed a high concentration of glibenclamide (107 μg/l, therapeutic range 10-150 μg/l). Three months after her operation she admitted that she had taken

glibenclamide tablets belonging to a relative. She had no previous psychiatric history but several stressful events had recently taken place. No overt psychiatric disorder could be identified, although she refused to be assessed formally by a psychiatrist. At follow up eight months after surgery she was free of hypoglycaemic symptoms and denied further sulphonylurea misuse, but she continued to have detectable serum glibenclamide concentrations (93 μg/l). Her motives and possible underlying psychiatric diagnosis remain unknown.

Discussion

Factitious hypoglycaemia is a rare cause of spontaneous hypoglycaemia in the United Kingdom.[2] Exogenous insulin administration is easily identified because of the concomitant suppression of C peptide. However, sulphonylurea misuse may mimic insulinoma because of the associated high insulin and C peptide concentrations. In a series of 151 cases investigated for spontaneous hypoglycaemia 5.3% of plasma samples submitted for insulin assay contained detectable concentrations of sulphonylurea drugs.[2] Patients with insulinoma often have raised proinsulin concentrations, but this feature is not diagnostic[2 3] and cannot exclude hypoglycaemia induced by sulphonylurea.

There is no ideal imaging technique for insulinoma. Computed tomography of the pancreas can successfully localise insulinomas in 20-80% of cases, but it rarely detects small insulinomas,[4] and false positive results may occur. Recent data indicate that magnetic resonance imaging of the pancreas may be a more sensitive alternative.[5] Coeliac axis angiography has been reported as correctly identifying the location of tumours in 50% of cases, with a false negative rate of 40%.[6] Intraoperative ultrasonogaphy in one series correctly identified all tumours that could not be palpated[7]; transhepatic portal venous sampling is particularly useful when the tumour cannot be identified by other means.[8] In our case false positive results in a computed tomogram and coeliac axis angiogram helped inform the decision to explore the patient's pancreas. In retrospect, her occupation should have raised the possibility of factitious hypoglycaemia,[9] although she had no psychiatric history, seemed sensible, and evoked sympathy rather than suspicion among medical and nursing staff. Inconsistencies in her clinical course were present in that the original fast failed to induce hypoglycaemia despite her symptoms at home, and some of the hypoglycaemic attacks occurred two hours after meals. Moreover, hypoglycaemia, which was intractable and required continuous intravenous dextrose infusion, ceased to be a problem in the immediate postoperative period, while the patient was bedbound and nursed intensively, and recurred as soon as she had to care for herself.

The dilemma the surgeon faces at laparotomy when no tumour can be identified is whether to perform a partial pancreatectomy or refrain from further surgical intervention. This case illustrates that partial pancreatectomy should not be performed if a tumour cannot be identified at operation. A distal pancreatectomy would be particularly unwise under these circumstances as an insulinoma in the body or tail of the pancreas is usually palpable, and if it is not apparent at laparotomy it is likely to be located in the head of the pancreas; a distal pancreatectomy would then be both ineffective and associated with substantial morbidity. In view of the lack of sensitivity and specificity of current preoperative imaging techniques it can be argued that biochemical confirmation of an insulinoma should be followed by laparotomy with intraoperative ultrasonography to detect tumours that are not palpable.

We conclude that insulinoma should not be diagnosed when the imaging results are equivocal, unless sulphonylurea misuse can be excluded by screening of plasma or urine taken at the time of hypoglycaemia, particularly if the patient has access to sulphonylurea drugs from a diabetic relative or has an occupation that facilitates access to them.[10]

We thank Dr G Beastall (Clinical Biochemistry, Glasgow Royal Infirmary) for performing the insulin and C peptide immunoassays, and Dr S Dawling (Poison's Unit Laboratory, Guy's and St Thomas' Hospital Trust, London) for the sulphonylurea screen.

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Correction

Fortnightly review: Screening for asymptomatic colorectal cancer

An editorial error occurred in this article by Hugh E Mulcahy and colleagues (25 January, pp 285-91). In table 1 (top of p 286) the lifetime risk of developing colorectal cancer for someone with more than two first degree relatives affected should have been > 1 in 3 (rather than 1 in 3).