

# Sickle-cell haemoglobin C disease in London

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**SYNOPSIS** The manifestations of the sickling disorders are becoming increasingly familiar to clinicians in Great Britain. One of these disorders, sickle-cell haemoglobin disease, has hitherto received little attention, being regarded as a relatively mild condition. This paper describes some of the distinctive clinical features of the disease as seen in a series of nine cases which have recently presented in London, two of which were fatal. The special hazards of the condition in relation to pregnancy, air travel, and general anaesthesia are discussed.

The increase in the immigrant population of Great Britain has caused a greater awareness among clinicians in this country of the manifestations of the sickling disorders. Sickle-cell anaemia, the most severe of these disorders, is now well known as a cause of chronic ill health in negro immigrants. The purpose of this article is to draw attention to another sickling disorder, sickle-cell haemoglobin C disease, which runs a somewhat different course. Disability is considerably less and the patient may enjoy normal health for a long period of time, only to suffer an unexpected and sometimes fatal sickling episode.

## The Sickling Disorders

The sickling disorders result from the inheritance of sickle-cell haemoglobin (haemoglobin S) either alone or in combination with other haemoglobin abnormalities. Haemoglobin S produces pathological effects by virtue of its property of forming long, rigid, rod-like structures within the red cell on deoxygenation. These deform the red cell into the characteristic sickle shape.

## SICKLE-CELL TRAIT

The inheritance of haemoglobin S from one parent gives rise to the heterozygous sickle-cell trait. The red cells contain roughly equal proportions of haemoglobins S and A. Deoxygenation does not cause sickling *in vitro* until PO<sub>2</sub> levels in the region of 10 mm Hg are reached (Griggs and Harris, 1956). Such a degree of tissue anoxia is highly unusual

although it may occur during anaesthetic accidents and flights in unpressurized aircraft. Sickle-cell trait is the commonest of the sickling syndromes. Haematuria caused by microinfarction of the kidney occurs in a small proportion of patients but the condition is generally symptomless.

## SICKLE-CELL ANAEMIA

The inheritance of haemoglobin S from both parents gives rise to the homozygous state, sickle-cell anaemia. Haemoglobin A is absent. The red cells sickle *in vitro* when the PO<sub>2</sub> of the blood is lowered to approximately 60 mm Hg (Griggs and Harris, 1956), a level reached at the venous end of capillary vessels. Sickled red cells are commonly observed in peripheral blood films. Because of the ease with which sickling occurs the clinical course is severe. Frequent infarctive episodes are superimposed upon a background of chronic haemolytic anaemia. Most patients are severely incapacitated and many die in childhood, although the prognosis appears to be more favourable in Jamaican than in African cases (Serjeant, Richards, Barbor, and Milner, 1968).

## SICKLE-CELL HAEMOGLOBIN C DISEASE

This is the third commonest sickling disorder in Great Britain. It arises from the inheritance of haemoglobin S from one parent and haemoglobin C from the other. The red cells sickle *in vitro* at PO<sub>2</sub> levels of about 30 mm Hg (Griggs and Harris, 1956). Intravascular sickling is therefore a less frequent occurrence than in sickle-cell anaemia. Sickle cells are unusual in peripheral blood films

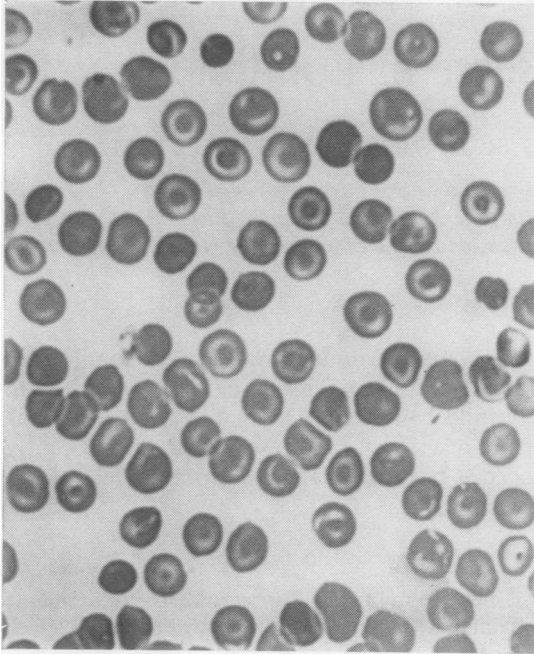


Fig. 1 *Blood film from a patient with sickle-cell haemoglobin C disease showing large numbers of target cells.*

which nearly always show large numbers of target cells (Fig. 1). The only other inherited condition in which comparable numbers of target cells are seen and which is likely to be encountered among negro immigrants is homozygous haemoglobin C disease where haemolysis is usually mild and sickling does not occur.

#### **Geographical Distribution of Haemoglobins S and C**

Haemoglobin S has its main distribution in tropical Africa. It is found throughout a vast area stretching from the Sahara in the north to the River Zambesi in the south. Carrier rates exceeding 20% are commonly found in this area. The distribution of haemoglobin C is much more restricted. It is mainly found within a small area of West Africa which includes Ghana and the western region of Nigeria and is bounded to the east by the River Niger (Lehmann and Nwokolo, 1959). The highest incidence is in northern Ghana where carrier rates of 20% have been reported (Edington and Lehmann, 1956). Sickle-cell haemoglobin C disease is mainly found in West Africa where the two areas coincide. It is also found in West Indian and American negro populations which originated from West Africa.

Chernoff (1955) states that about 1 in 1,500 of the negro population of the North American continent has sickle-cell haemoglobin C disease. The incidence is probably similar among West Indians in Great Britain.

#### **Case Reports**

The case reports which follow were chosen to illustrate some of the characteristic features of the disease.

##### **CASE 1: RECURRENT UPPER RESPIRATORY INFECTIONS IN A CHILD**

A 3½-year-old Nigerian boy presented with a series of upper respiratory tract infections. He was noted to be pale and to have moderate enlargement of the spleen. Haematological investigations showed anaemia (haemoglobin 7.2 g/100 ml), with many target cells, some polychromatic cells, and a few sickle cells. The white cell and platelet counts were normal. The sickle test was positive and haemoglobin electrophoresis revealed haemoglobins S and C.

He has not so far suffered any serious infarctive episode.



Fig. 2 *Radiograph of right hip (case 2) showing changes suggestive of aseptic necrosis of the head of the femur.*

**CASE 2: ASEPTIC NECROSIS OF THE HEAD OF THE FEMUR**

A 29-year-old male law student from Nigeria was found to have sickle-cell haemoglobin C disease by chance. His haemoglobin was examined by electrophoresis after an abnormal haemoglobin had been found in his child's blood during a survey. Five years earlier after an accident he suffered chronic pain in the hip which was eventually relieved by arthrodesis. A radiograph of the hip later before operation (Fig. 2) shows features compatible with aseptic necrosis of the head of the femur although at the time a diagnosis of osteoarthritis was made.

Apart from his hip, the only positive findings on physical examination were moderate splenomegaly and a minor degree of sickle-cell haemoglobin C retinopathy (see case 6). His haemoglobin level was 12.5 g/100 ml. The blood film showed large numbers of target cells.

**CASE 3: BONE PAIN, GALLSTONES**

A 24-year-old female immigrant from British Guiana had been ill for two days with backache, pain in the right wrist, and fever. She had suffered intermittent attacks of joint pain since childhood. The spleen was not palpable.

The haemoglobin level was 10.4 g/100 ml, the total white cell count 8,000/c mm, and the blood

film showed characteristic abnormalities in the femoral shafts and vertebral bodies (Fig. 3); a cholecystogram, performed on account of slight tenderness under the right costal margin, showed the presence of multiple radiotranslucent gallstones.

**CASE 4: ABDOMINAL PAIN DURING PREGNANCY WITH INTRAUTERINE DEATH OF THE FOETUS**

A 29-year-old Jamaican was first seen in early pregnancy. Six previous pregnancies had all been normal. The haemoglobin level was 10.5 g/100 ml. A routine sickle test was positive and haemoglobin electrophoresis showed haemoglobins S and C. The spleen was not palpable.

When 32 weeks pregnant she was admitted to hospital with left-sided abdominal pain. She became jaundiced and febrile with marked tenderness under the left costal margin. The haemoglobin dropped to 3.5 g/100 ml, reticulocyte count was 19%, and methaemalbumin was detected in the plasma. A sickling crisis was diagnosed and 2 pints of blood transfused. The next day she passed only 200 ml of urine, her blood urea rose from 30 mg to 80 mg/100 ml, and the serum bilirubin was 17 mg/100 ml. Radiographs of the abdomen showed multiple fluid levels.

At laparotomy the spleen was found to be enlarged with purple areas suggesting recent infarction. The



Fig. 3a



Fig. 3b

Fig. 3a Radiograph of lumbar spine (case 3) showing biconcave deformity of the vertebral bodies.

Fig. 3b Radiograph of upper part of right femur (case 3) showing changes secondary to bone marrow hyperplasia. Diffuse lucencies are present.

whole of the small intestine was congested. No pulsation could be detected in any of the small mesenteric vessels and the veins were distended but did not appear to be thrombosed. A lower segment Caesarean section was performed and a dead baby was removed. The postoperative treatment included intravenous heparin and magnesium sulphate.

Following the operation the output of urine increased but the blood urea rose to 190 mg/100 ml, and the serum bilirubin reached a maximum of 33 mg/100 ml before returning to normal.

#### CASE 5: MATERNAL DEATH FOLLOWING POST-PARTUM COLLAPSE

A 24-year-old West Indian was admitted to hospital when 37 weeks pregnant complaining of severe pains in both knees and in the back. She had been attending the antenatal clinic where sickle-cell haemoglobin C disease had been diagnosed. She gave a history of poor health for many years with pains in the head and abdomen.

Eleven days later she complained of severe chest pain and difficulty in breathing, and a sickling crisis was suspected. Her haemoglobin was 7.5 g/100 ml. Labour began spontaneously at 39 weeks. After forceps delivery under local anaesthesia she was restless, with a pulse rate of 120/min and a blood pressure of 90/60 mm Hg; 15 mg morphine was given together with magnesium sulphate. Six hours later the patient suddenly became shocked and died.

Postmortem examination showed generalized pulmonary oedema but no pulmonary emboli. There was slight dilatation of the right side of the heart but no other abnormality. The spleen was enlarged, weighing 1,070 g, and intensely congested but not infarcted.

#### CASE 6: SICKLE-CELL HAEMOGLOBIN C RETINOPATHY WITH VITREOUS HAEMORRHAGE

A 21-year-old Jamaican presented with sudden blurring of vision in the left eye. Examination of the eye revealed a vitreous haemorrhage. Thirty-six hours later vision in the left eye had deteriorated to counting fingers at 3 feet. The left fundus now showed a large retinal and preretinal haemorrhage. The peripheral retinal arterioles were tortuous. Extra arcades of arteriovenous anastomoses, occasional tufts of new vessels, and areas of chorio-retinal atrophy were seen in the periphery of both fundi. Conjunctival vessel anomalies were present. The spleen was palpable. The haemoglobin was 12.3 g/100 ml. The sickle test was positive and haemoglobin electrophoresis showed haemoglobins S and C.

After six weeks' bed rest vision in the left eye had returned to normal.

The patient gave a history of pregnancy complicated by right hip pain and pyrexia in the puerperium. The hips were examined radiographically and changes suggestive of early avascular necrosis of the head of the right femur were found.

#### CASE 7: PAINLESS HAEMATURIA

A 28-year-old Nigerian presented with gross painless haematuria. He had never had any urinary symptom before but had experienced occasional bouts of jaundice and fever.

The spleen was not palpable. Microscopy and culture of the urine revealed no organisms. No schistosoma ova were found in the urine. Haemoglobin was 13.6 g/100 ml; white cell count normal; the blood film showed numerous target and occasional sickle cells. The sickle test was positive and haemoglobin electrophoresis showed haemoglobins S and C.

Both kidneys appeared normal on intravenous pyelography. The bladder was not well defined, possibly owing to the presence of blood. No bone abnormality was present. Cystoscopy was arranged but the patient defaulted. Two years later the patient was seen again in another department of the hospital complaining of pain in the right hip on walking. He had had no recurrence of haematuria.

#### CASE 8: DEATH FOLLOWING GENERAL ANAESTHESIA

A 40-year-old Ghanaian noticed a slight deterioration in visual acuity in both eyes for about a year. Examination showed the presence of retinal detachments in the periphery of both optic fundi together with changes suggestive of sickle-cell haemoglobin C retinopathy, which was confirmed by haemoglobin electrophoresis. He was admitted for photocoagulation of the abnormal vessels in the periphery of the fundi. The operation was carried out under general anaesthesia, care being taken to prevent hypoxaemia. Soon after his return to the ward the patient's breathing was noted to be 'bubbly'; a new airway was inserted but he failed to regain full consciousness. The haemoglobin was 8.5 g/100 ml and the blood film showed numerous target cells and occasional sickle cells. A sickling crisis was diagnosed and treatment with hyperbaric oxygen was begun but the patient died.

Postmortem examination showed intense vascular congestion of all organs. There were numerous microinfarcts in the brain stem and the main pulmonary arteries contained antemortem thrombus.

**CASE 9: SPLENIC INFARCTION DURING AIR TRAVEL**

A 14-year-old schoolgirl from Jamaica was admitted to hospital with acute abdominal pain which started during a flight to London. It was noted that the spleen was enlarged and tender. The haemoglobin was 11.5 g/100 ml; white cell count 11,100/c mm; reticulocyte count 5.6%; mild polychromasia and many target cells were noted; the sickle test was positive, and haemoglobin electrophoresis showed haemoglobins S and C.

A diagnosis of splenic infarction was made and the patient made an uneventful recovery.

**Discussion**

The commonest complaint among 60 patients with sickle-cell haemoglobin C disease studied by River, Robbins, and Schwartz (1961) was bone and joint pain, followed by abdominal pain and chest pain. Other complaints such as haematuria, jaundice, leg ulcers, visual disturbances, headache, fits, priapism, epistaxis, and sickling crises during pregnancy were considerably less frequent. The symptomatology of sickle-cell anaemia is very similar. Indeed, from the clinical point of view the two conditions are often thought of as differing only in their degree of severity, sickle-cell haemoglobin C disease being the more benign. It would be a mistake to accept this view uncritically. Two of our patients died and some of the others were seriously ill. Onuaguluchi and Akande (1966) reported three non-pregnant patients who had very severe sickling crises, two of whom died.

The most important differences between the two conditions are that sickling incidents are considerably less frequent in sickle-cell haemoglobin C disease and that the patient is usually fit between such incidents. Smith and Conley (1954) reported an exceptional patient who experienced no symptoms referable to sickling until the age of 70 years. In contrast, most patients with sickle-cell anaemia are chronically ill from early childhood. Sickle-cell haemoglobin C disease is further distinguished from sickle-cell anaemia by the unusual number of sickling crises at the time of parturition, by the high incidence of bone infarction, particularly of the head of the femur and humerus, and by the occurrence of a peculiar retinopathy which is often complicated by vitreous haemorrhage.

Because the main cause of symptoms is the occurrence of scattered infarcts, the presentation and history are often polysymptomatic, and an initial diagnosis of hysteria is not infrequent. Occasionally the diagnosis is first made during a quiescent phase of the disease by the chance

discovery of target cells in the peripheral blood or of splenomegaly. Fifteen out of the 75 patients studied by River *et al* (1961) were diagnosed in this way.

Some of the more important manifestations of the disease are discussed below.

**MUSCLE, BONE, AND JOINT PAIN**

Skeletal pain due to bone infarction is the commonest complaint in sickle-cell haemoglobin C disease. Patients often say they have had rheumatism since childhood. The radiological changes in bone infarction are variable. In many cases no changes are seen. A small infarct in a long bone may appear as an area of increased density. Massive infarction of the shaft of a long bone, especially in a child, may produce extensive subperiosteal new bone formation, which may eventually result in a 'bone with a bone' appearance (Cockshott, 1965). Infarcts sometimes become infected, especially with bowel organisms of the Salmonella group, resulting in a low-grade osteomyelitis.

The infarction of bone under the cartilage of a joint causes arthralgia and, if the bone is weight-bearing, subchondral collapse. When the head of the femur is involved, a form of aseptic necrosis with chronic hip pain develops, as in case 2 (Fig. 2). The complication should be suspected in all negro patients with continuous hip or low back pain. Radiologically the hip lesion bears a superficial resemblance to Perthe's disease, the main difference being that usually only a part of the head of the femur is involved and that the lesion is more common at a later age after the epiphysis has fused (Barton and Cockshott, 1962). The head of the humerus is sometimes affected similarly.

Some patients show the radiological changes of bone marrow hyperplasia due to chronic haemolysis. The changes are mild and are best seen in the vertebral bodies (Becker, 1962) which may show coarsening of the trabecular pattern and, occasionally, cupping of the articular surfaces (Fig. 3).

**ABDOMINAL OR CHEST PAIN**

Abdominal pain is a common mode of presentation. The pain is cramping or aching, is poorly localized, and is often accompanied by diffuse abdominal tenderness. When severe it suggests an acute surgical emergency. The danger is that an unnecessary laparotomy may be performed which will worsen the patient's condition. The possibility of splenic infarction or gallstones should be considered.

The life span of the red cell in sickle-cell haemoglobin C disease is about half normal (Movitt, Mangum, and Porter, 1963). There is thus a mild chronic haemolytic state and the resulting increase

in bile pigment excretion occasionally leads to cholelithiasis. Eight per cent of the patients studied by River *et al* (1961) were known to have gallstones.

None of our patients presented with chest pain although this has been a widely recorded symptom. Chest pain is caused by pulmonary infarction which may be the result of tangled sickle cells or marrow embolism (Mosser and Shea, 1957; Shelley and Curtis, 1958; Ober, Bruno, Simon, and Weiner, 1959).

#### VISUAL DISTURBANCE

Sudden impairment of vision due to vitreous haemorrhage is a frequent presenting symptom in patients with sickle-cell haemoglobin C disease (Konotey-Ahulu, 1968). The bleeding originates in vascular abnormalities which lie mainly at the periphery of the fundus. Comma-shaped dilatations of the conjunctival vessels are often found in patients with sickle-cell anaemia and sickle-cell haemoglobin C disease (Paton, 1962).

#### HAEMATURIA

Haematuria due to micro-infarction of the kidney occurs in all the sickling syndromes. The fact that it is seen in sickle-cell trait suggests that the physiological milieu in the blood vessels of the kidney is particularly favourable to sickling. Haematuria in sickle-cell haemoglobin C disease was reviewed by Chapman, Reeder, Friedman, and Baker (1955). It is characteristically gross and painless, ceasing spontaneously but tending to recur.

#### PREGNANCY

Pregnancy is hazardous in sickle-cell haemoglobin C disease. Maternal mortality rates have varied widely in different series but figures as high as 21% have been quoted (Eisenstein, Posner, and Friedman, 1956). In some series the mortality rate has been inflated by the inclusion of patients admitted in a terminal state. Fullerton, Hendrickse, and Watson-Williams (1965) followed 190 pregnancies in Ibadan, Nigeria, and concluded that the 'natural' maternal mortality rate was probably about 10%, a figure which they were able to reduce to 2.4% in the latter part of their series by clinical supervision and folic acid supplements.

There have been numerous reports of sudden death in crisis during pregnancy (Edington, 1957; Shelley and Curtis, 1958; Fullerton *et al*, 1965). The risk appears to increase near term and to reach a maximum during labour and immediately afterwards. In many cases the first symptom of crisis is bone pain. The sequence of events which leads to death in crisis is not fully understood. The Ibadan workers considered that most of their deaths were

due to marrow and fat embolism from infarcted areas of bone but they stated that the postmortem evidence for this was not always satisfactory. There was no evidence of marrow embolism in case 5 in the present series.

#### SPLENOMEGALY

Splenic enlargement is one of the features that distinguishes sickle-cell haemoglobin C disease from sickle-cell anaemia. It was present in two-thirds of the patients studied by River, Robbins, and Schwartz (1961).

Splenic infarction during air travel due to the hypoxaemia of altitude is a well known hazard in the sickling disorders (Smith and Conley, 1955; Coleman and Furth, 1956).

The case reported here occurred in a pressurized aircraft. It is often assumed, wrongly, that significant hypoxia does not occur in such aircraft. However in most modern civil airliners the 'cabin altitude' is equivalent to 5-7,000 feet when the aircraft is flying at its normal cruising altitude of 30-40,000 feet.

#### ANAESTHESIA

General anaesthesia can cause intravascular sickling in all of the sickling syndromes. The literature is reviewed and the management of anaesthesia is discussed in two papers by Gilbertson (1965, 1966). Hypoxaemia is the chief danger. There is little risk of hypoxaemia while the anaesthetic is being given, but greater risk arises during recovery.

Konotey-Ahulu (1969) believes that the dangers of general anaesthesia in the sickling disorders are underestimated in Great Britain. He considers it essential to perform the sickle test before considering any surgical procedure on a patient of African descent.

#### SICKLE-CELL HAEMOGLOBIN C DISEASE IN CHILDREN

The manifestations of the disease in children were reviewed by Tuttle and Koch (1960). Painful crises were experienced by most of their patients, the average age of onset being 4 years. The commonest complaint was of bone and joint pains which in some cases simulated the migratory arthralgia of acute rheumatic fever (Lisker, Finkelstein, Schwartz, Marulyali and Valdes-Dapena, 1965). Abdominal crises occurred less frequently. Many children, like case 1 in the present series, were subject to repeated upper respiratory infections, which often preceded crises.

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