Sickle cell anaemia

General

Sickle cells are much less flexible than normal erythrocytes. They therefore have difficulty in passing through capillary vessels, the diameter of which is often less than half the diameter of a red blood cell. Janet Watson noted that symptoms appeared in infants only after concentrations of fetal haemoglobin (Hb F) had fallen, establishing the notion of the beneficial effect of Hb F on disease manifestations.

Sickle cell anaemia, haemoglobin

Haemoglobin structure

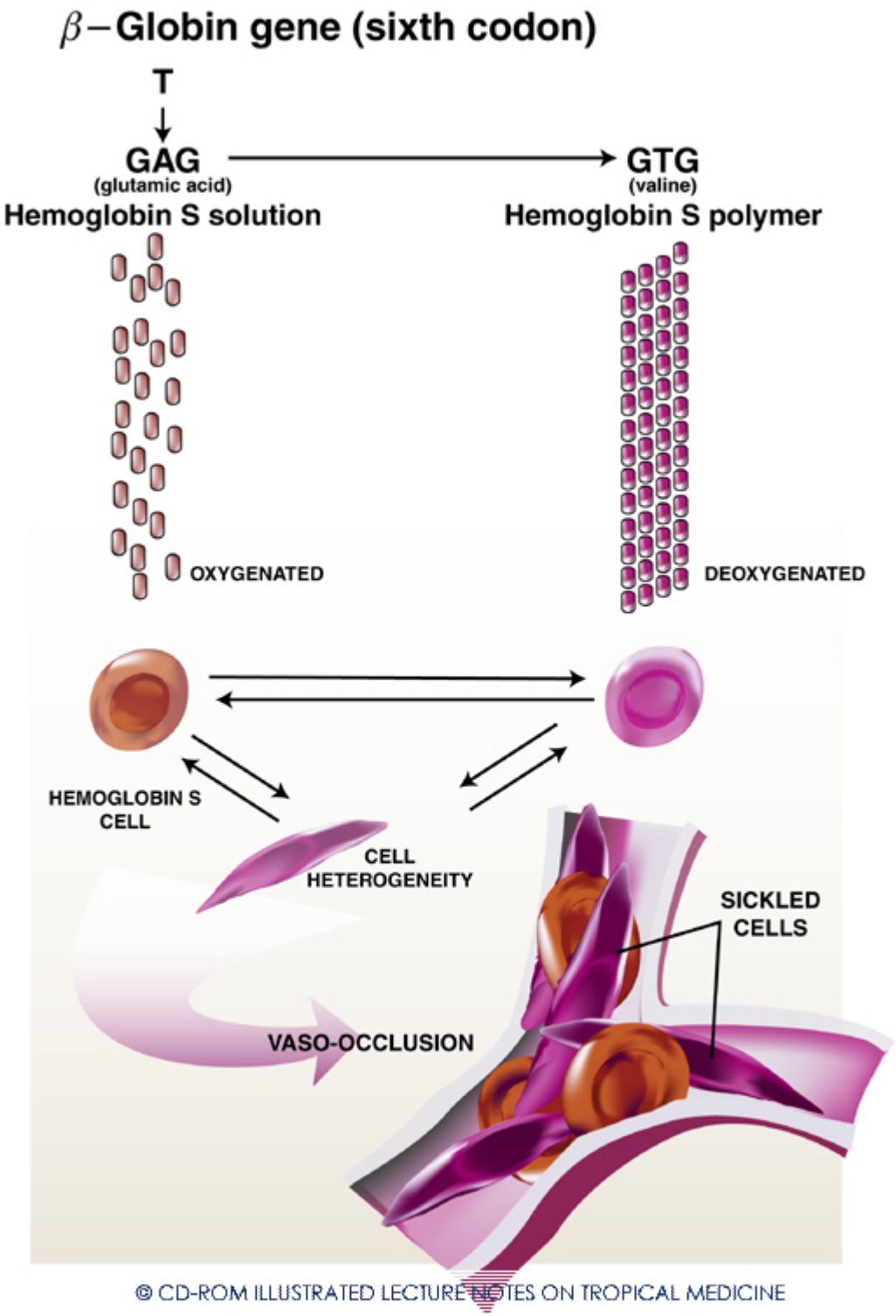
Each molecule of haemoglobin consists of a tetramer consisting of 2 pairs of polypeptide chains to which a total of 4 haem groups (one haem group per globin chain) is linked. One molecule of haemoglobin therefore contains 4 proteins. Hb A contains 2 globin chains of one type (alpha) and 2 globin chains of another type (beta Depending on which 4 chains are present in the haemoglobin tetramer, the molecule is given its name.

There are many haemoglobin variants:

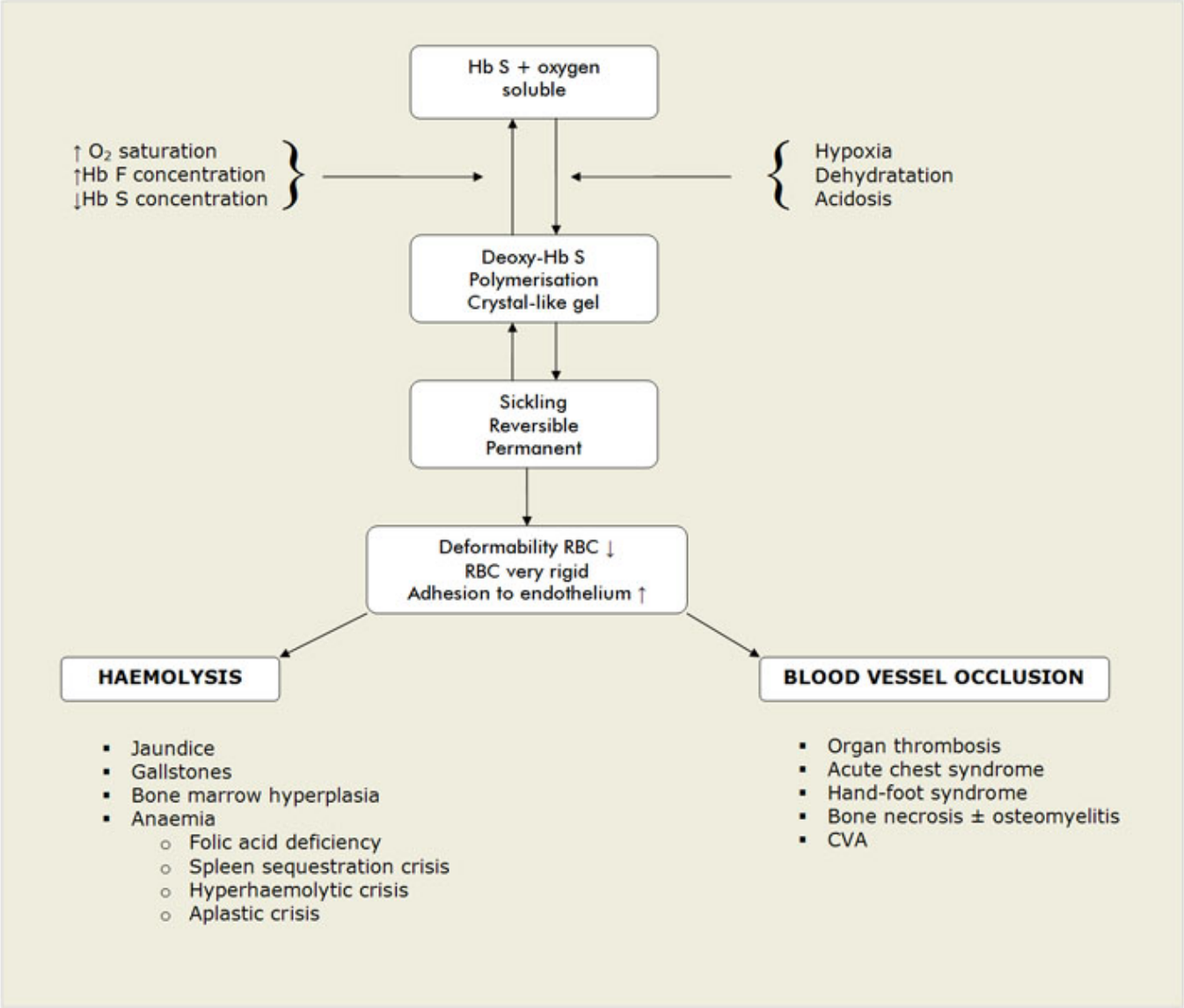
Normal
Hb A: alpha $_2$beta$_2$
Hb A2: alpha$_2$delta$_2$
Hb F: alpha$_2$ gamma$_2$

Pathological
Hb S: alpha$_2$ beta$_2^S$
Hb C: alpha$_2$ beta$_2^C$
Hb E: alpha$_2$ beta$_2^E$
Hb H: beta$_4$ (see alpha-thalassemia)
Hb Barts: gamma $_4$

Physiopathology



Pathophysiology of sickle cell anaemia. Deoxy-haemoglobin S undergoes time-dependent polymerisation. This changes the shape of the red blood cells, which can block the microcirculation.
Adapted from a drawing in New England Journal of Medicine, 2002.



The normal haemoglobin of a child or an adult are Hb A (97%), Hb A_2 (2%) and Hb F (1%). Hb A contains 2 alpha-chains and 2 beta-chains. If by mutation, the 6th amino acid of the ß-chain (glutamic acid, negatively charged) is replaced by a different amino acid (valine,

hydrophobic), Hb S is formed. As a result a hydrophobic site is formed on the outside of the folded mutated beta chain. With normal arterial oxygen tension there is no problem and the molecule transports the oxygen. In the capillary bed in the tissues the oxygen is released and deoxyhaemoglobin S is formed. This latter substance has several different properties. In deoxy-Hb S there is a second hydrophobic site on the surface. This site is concealed in oxy-Hb S. The site is complementary to the first. These two hydrophobic regions adhere to each other, resulting in a kind of polymerization of the deoxyhaemoglobin S molecules. The hydrophobic valine on the surface makes the haemoglobin molecule somewhat less water-soluble if the molecule is not bound to oxygen. The concentration of haemoglobin in the erythrocyte (32-34 g %) does however require a very water-soluble molecule. The deoxyhaemoglobin S molecules start to come out of solution (precipitate). At low oxygen concentrations the deoxyhaemoglobin S molecules adhere to each other, forming long, rigid strands and thus deform the red blood cells making them more rigid. The molecules stick to each other in a definite pattern (like a crystal). This polymerization reaction is relatively slow, giving a “delay time” or T_d. The slower the circulation and therefore the longer the time before reoxygenation in the lungs, the more sickling occurs. Usually the transit time of a red blood cell in the microcirculation is less than T_d and a major catastrophe is avoided.

The main variables that affect sickling are the intracellular haemoglobin concentration, pH, the level of oxygenation and the percentage of Hb F. Sickling is accelerated by lack of oxygen, slow blood circulation, acidification and dehydration (a situation which is common with infections). The formation of rigid Hb SS strands is counteracted by Hb F (efficiency of polymerization is reduced). People with high concentrations of Hb F have far fewer symptoms than patients with low Hb F concentrations.

The sickling process also causes damage to various membrane proteins of the erythrocyte, thus promoting adhesion to the vascular endothelium. This makes circulation even more difficult. The degree of adherence is closely correlated to the severity of the disease. If there is inflammation, this “stickiness” can increase even more.

Additional factors play a part in the pathophysiology of sickle cell disease: endothelial cells can be “activated” i.e. they can be induced to express all kinds of molecules on their membrane, after exposure to various inflammatory substances (cytokines, prostacyclin’s, etc). Such cells become “sticky” and promote local haemostasis and possibly thrombosis.

There is also an increase in the number of adhesion molecules on the red blood cells. The local production of Nitric oxide (NO) by the damaged endothelium falls.

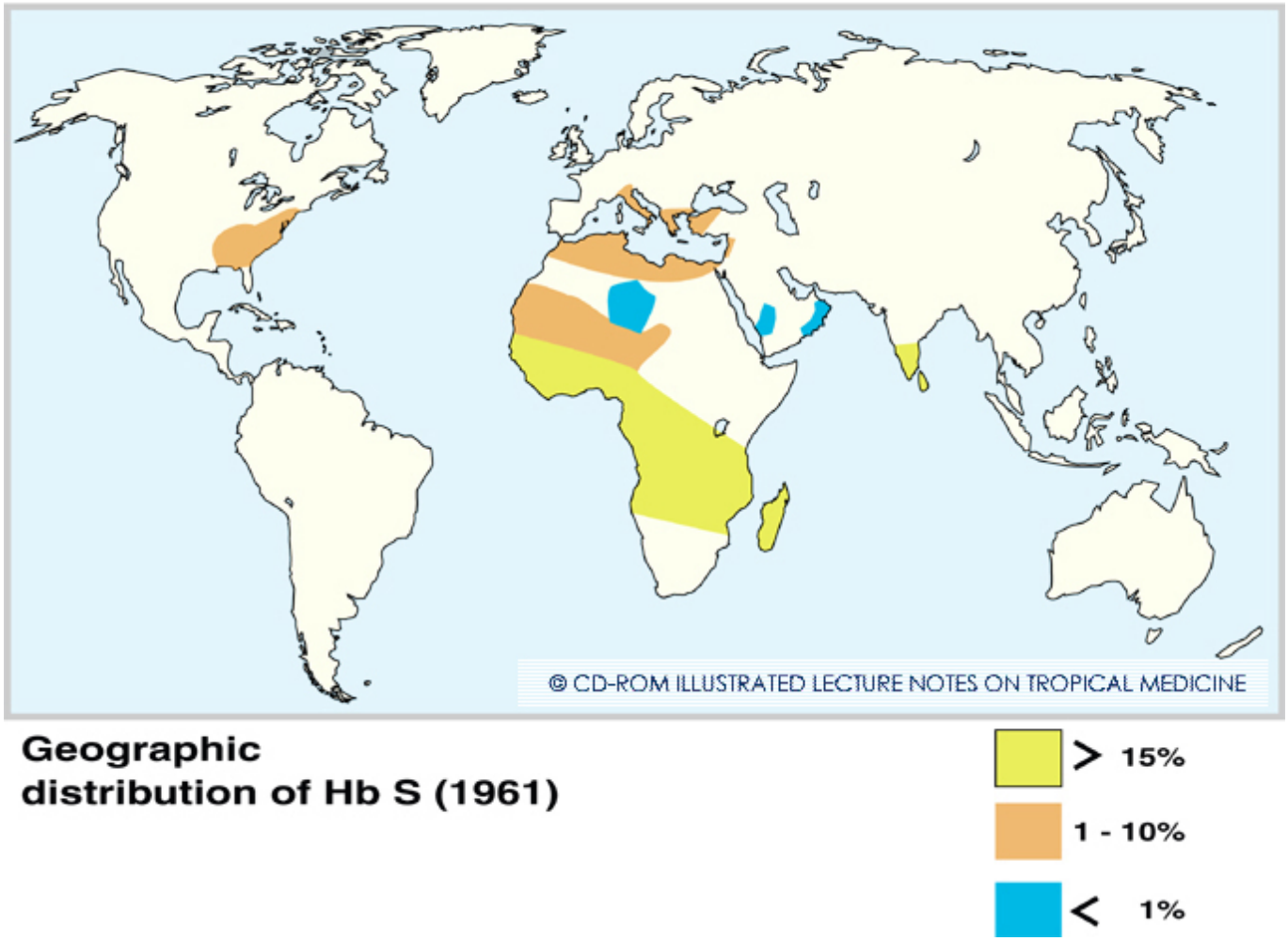
Nitric oxide function

Nitric oxide (NO) produced by endothelial cells causes vasodilatation (effect is concentration dependent). Free haemoglobin in plasma will capture NO, thereby diverting nitric oxide from its homeostatic vascular function.

What are the clinical consequences of sickling?

- Sickle cells rapidly haemolyse. As a result, anaemia occurs: sickle cell anaemia.
- Sickle cells are rigid and obstruct the microcirculation. As a result, small or large infarctions can occur.
- Tissues with poor blood circulation can be infected more easily.
- Due to splenic atrophy, resistance to certain pathogens is reduced.

Geographical distribution



Map sickle cell disease (drepanocytosis). Due to the slave trade, the disease also exists in North America, but is especially common in areas where Plasmodium falciparum is frequent. Copyright ITM

The sickle cell gene occurs in large parts of Africa and to a somewhat lesser extent in the Middle East (Saudi Arabia) and India. In West Africa, 5 to 25% of the population are carriers of the gene. In Central and East Africa, heterozygotes occur with a frequency of from 20 to 40%. If 20% of the population are carriers of the gene, it follows that 1% of newborn children will be homozygous. Through the slave trade the sickle cell gene also found its way to North and

South America.

Heterozygous carriers are relatively protected against fatal *P. falciparum* malaria. They are infected just as often, but are less likely to die from the infection. If the malaria parasite is present within the erythrocyte, the red blood cell acidifies slightly. This is enough to promote sickling. Because of the damage to the membrane; potassium flows out of the red blood cell, which is damaging to the parasite and the erythrocyte. The red blood cell is rapidly destroyed, for example in the spleen (heterozygotes have a normal spleen). Since heterozygotes in an endemic malaria area have a longer life expectancy than people with normal haemoglobin, it is thought that this has promoted the occurrence of sickle cell haemoglobin in Africa over the course of evolution. On the other hand, homozygous Hb S people have a very low life expectancy. There will therefore be a genetic equilibrium.

Sickle cell anaemia, genetics and heredity

Sickle cell anaemia is a genetically determined disease. A distinction is made between three main groups: homozygotes, heterozygotes and double heterozygotes.

Hb SS disease: classic sickle cell anaemia

Hb AS: sickle cell trait, heterozygote

Hb S/Beta°-thalassemia; Hb SC: severe double heterozygote; phenotypical similar as Hb SS

Heterozygosity (“sickle cell trait”)

If someone has both a normal gene (from one parent) and a mutated gene (from the other parent), they produces both the normal haemoglobin (Hb A) and also the sickle cell haemoglobin (Hb S). One would expect a heterozygote HB AS to have about 50% haemoglobin A and about 50% haemoglobin S, but for a variety of reasons, the average patient has about 2/3 Hb A and 1/3 Hb S. The person is an asymptomatic carrier and each red blood cell contains both Hb A and Hb S. Such erythrocytes are functionally normal and have the advantage that they provide relative protection against fatal *Plasmodium falciparum* infection. Heterozygotes lead a normal life. But they may well pass the gene on to their

children

Probability per child of having the different haemoglobins:

Parent Hb AA x Parent Hb AS –> 50% probability of Hb AA and 50% probability of Hb AS

Parent Hb AS x Parent Hb AS –> 25% probability of Hb AA, 25% probability of Hb SS and 50% probability of Hb AS

Homozygosity

If a patient has two identical mutated genes (homozygote) they cannot produce Hb A. After birth, the Hb F concentration falls and after 3 to 6 months, the red blood cells contain mainly haemoglobin Hb S. This will lead to sickle cell disease.

Double heterozygotes

Certain double heterozygotes can display a sickle cell phenotype.

1. haemoglobin SC
2. haemoglobin SD
3. haemoglobin SO Arab
4. haemoglobin S beta thalassemia
5. haemoglobin S with haemoglobin New York

Sometimes a child has both a sickle cell gene and also a gene for haemoglobin C. It then has both haemoglobin S and haemoglobin C (Hb SC). Doubly heterozygous people suffer a less serious course of the disease than homozygous sickle anaemia patients. They have a clearly increased risk of eye damage (retinitis proliferans), avascular necrosis of the head of the femur, haematuria and complications during pregnancy (pulmonary infarction and risk of fat embolism after bone marrow infarction).

A little caveat: patient who are homozygous for Hb SS can have Hb A in their blood after a blood transfusion. Don’t be misled by this.

Clinical aspects

It is possible to distinguish two clinical phenotypes of sickle cell disease. The first is dominated by haemolysis and is characterized by severe haemolytic anaemia, leg ulcers (especially lower legs and around ankles) and pulmonary hypertension. The second is dominated by vaso-occlusion incidents, with episodic painful crises, acute chest syndrome, splenic infarction leading to functional asplenia, stroke and avascular necrosis of joints (hip, humerus) predominate.

Vaso-occlusive complications

Pain episodes	In more than 70% of patients.
CVA	In 10% of children; “silent” lesions with cognitive damage in 50-90%.
Acute chest syndrome	In 40% of patients, more often in children.
Priapism	In 10-40% of men. Severe cases lead to permanent dysfunction.
Liver disease	In <2%. Multiple causes: hep B, C, iron overload.
Spleen sequestration	In children < 6 years of age. Often preceded by infection.
Spontaneous abortion	In 6% of pregnant women.
Skin ulcers (leg)	In 20% of adults
Osteonecrosis	In 10-50% of adults (often femur, humerus).
Proliferative retinopathy	Rare in sickle cell anaemia; in 50% with Hb SC.
Renal insufficiency	In 5-20% of adults, often with severe anaemia.

Complications of haemolysis

Anaemia	Haematocrit often 15-30%.
Gallstones	In the majority of adults, usually asymptomatic.
Red bone marrow	Expansion leads to weakened cortical bone.

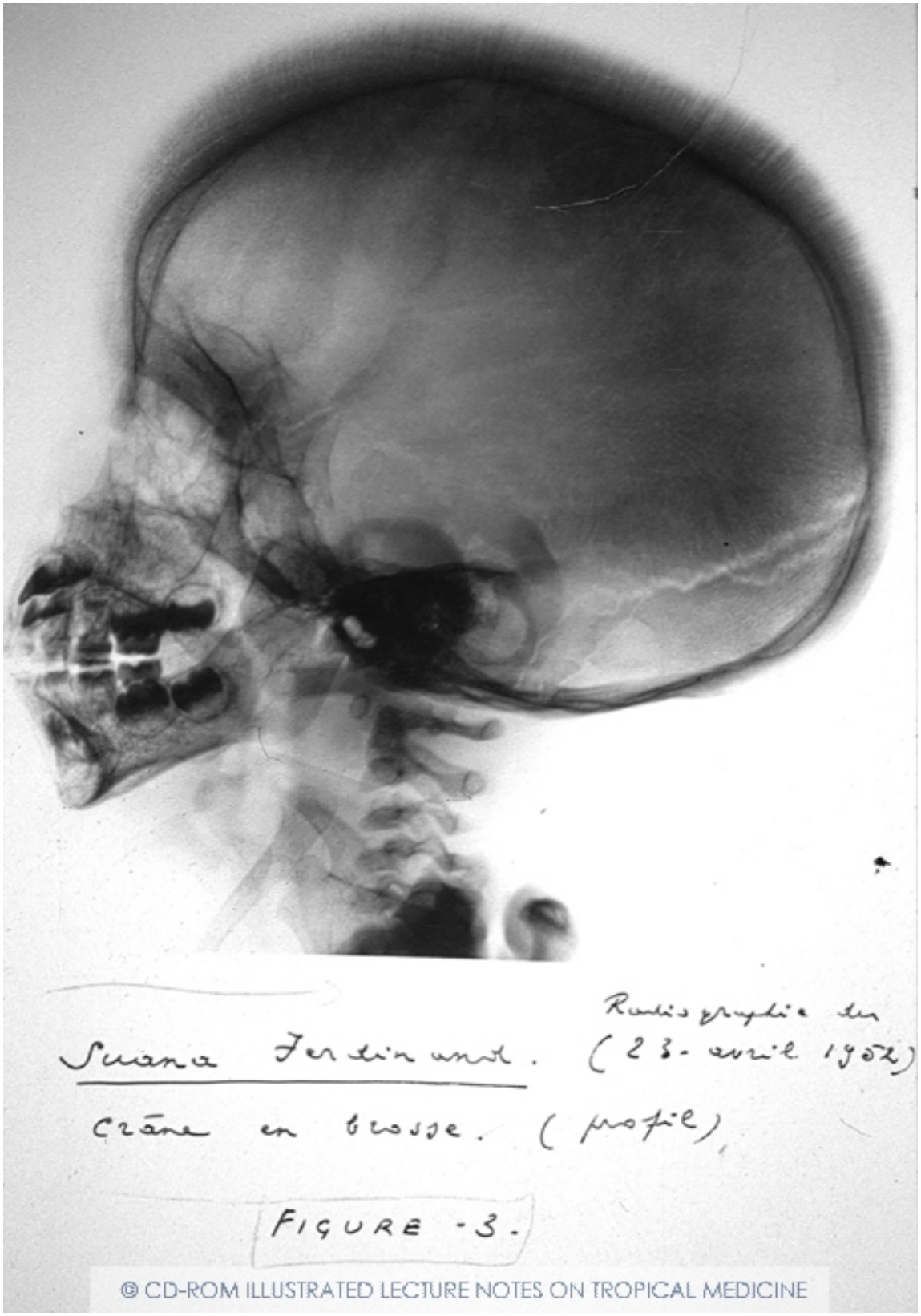
Infectious complications

Streptococcus pneumoniae	Sepsis in 10% of children < 5 years.
Osteomyelitis	Often by Salmonella or Staphylococcus aureus.
Escherichia coli sepsis	In adults often originating from infection of the urinary tract.
Acute aplastic crisis	Due to parvovirus B19. Sudden severe anaemia.

Individuals with sickle cell trait are generally asymptomatic and have no abnormal physical findings. Their laboratory evaluation often shows microcytosis but is otherwise normal with no anaemia, no evidence of haemolysis and no laboratory abnormalities other than haemoglobin AS on haemoglobin electrophoresis. Complications such as splenic infarction, pain episodes and sudden death may be induced by severe hypoxia, severe dehydration, and exertion at the limits of human endurance, e.g. at high altitudes.

Homozygous (Hb SS) children with little Hb F have the clearest symptoms. The symptoms result from haemolysis, thromboses, infections and acute haematological crises. In rural Africa only a few survive beyond puberty. In the first few months after birth the baby is virtually normal (the Hb F concentration is still high). The first problems start at about 3 to 6 months.

Haemolysis


Radiographie du
(23 avril 1902)
Suana Ferdinand.
crâne en bosse. (profil)
FIGURE -3.
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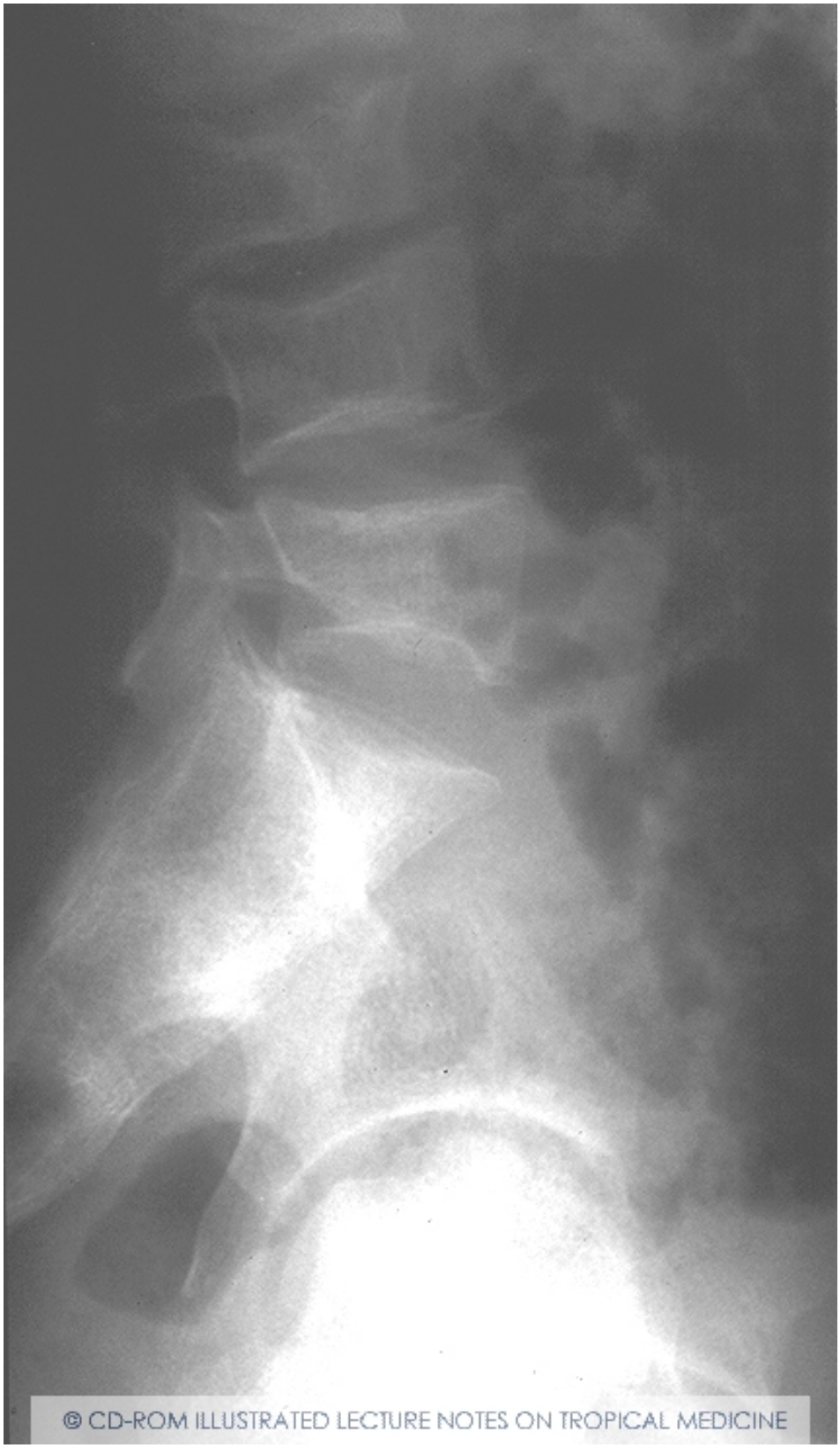
”Hair-on-ends” image caused by bone marrow expansion in the diploic space in chronic haemolytic diseases, such as sickle cell anaemia or more commonly in beta thalassemia major. The major trabecular spicules in the diploë are aligned perpendicular to the inner table in an effort to support the soft outer table. Photo ITM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Fish vertebrae in sickle cell anaemia. Marrow expansion makes the vertebrae more susceptible to compression, leading to this diabolo-shape. Copyright ITM

Chronic haemolysis manifests itself as pallor, mild jaundice, dark urine and retarded growth. There is hypertrophy of the bone marrow, which can often be seen in the cranium and the maxillae. But the expansion of the bone marrow is less pronounced than in homozygous ß-thalassemia, possibly because less erythropoietin is produced than expected due to repeated kidney damage. Due to the constant haemolysis and the production of bilirubin; bilirubin gallstones are produced at a very young age (such stones are often not radio-opaque). There is splenomegaly up to about 5 years, afterwards there is atrophy because of the repeated infarctions of the spleen. The expansion of the bone marrow can usually be seen clearly by frontal “bossing”, a pronounced curving of the forehead and by widely spaced teeth in the jaws. On an X-ray of the cranium, small canals in the diploë of the vault of the cranium and are known as a “hair-on-end” appearance (see Fig).

Acute haematological crisis

Haematological crises sometimes occur. In children aged from 6 months to 3 years the spleen can sometimes swell acutely (sequestration of blood in the spleen), with sudden anaemia, hypovolemia and shock as a result. Many do not survive this. Due to infections, such as malaria for example, hyperhaemolysis can occur. After certain viral infections (for example parvovirus B19) a period may follow during which the bone marrow does not form any new red blood cells (aplastic crisis). Bone marrow arrest can also occur if there is a marked folic acid deficiency.

Thrombosis

Thrombosis is manifested most commonly as episodes of pain but also can produce kidney infarctions (haematuria, papillary necrosis), priapism, atrophy of the spleen, bone necrosis (head of the femur, head of the humerus, metacarpals, vertebrae), cerebrovascular accident (CVA), including the rather rare Moyamoya syndrome (collateral circulation developing around blocked vessels, these collateral vessels are prone to bleeding aneurysm and thrombosis; moyamoya means “puff of smoke” in Japanese referring to the appearance of the

collateral vessels on MRI), chronic skin wounds (mainly on the shins) and proliferative retinopathy. Hand-foot syndrome is sometimes the first clinical manifestation. The child then has acutely painfully swollen hands and feet. Chronic damage to the vertebrae leads to biconcave vertebrae (“fish vertebrae”; see Fig) with a typical appearance on X-ray.

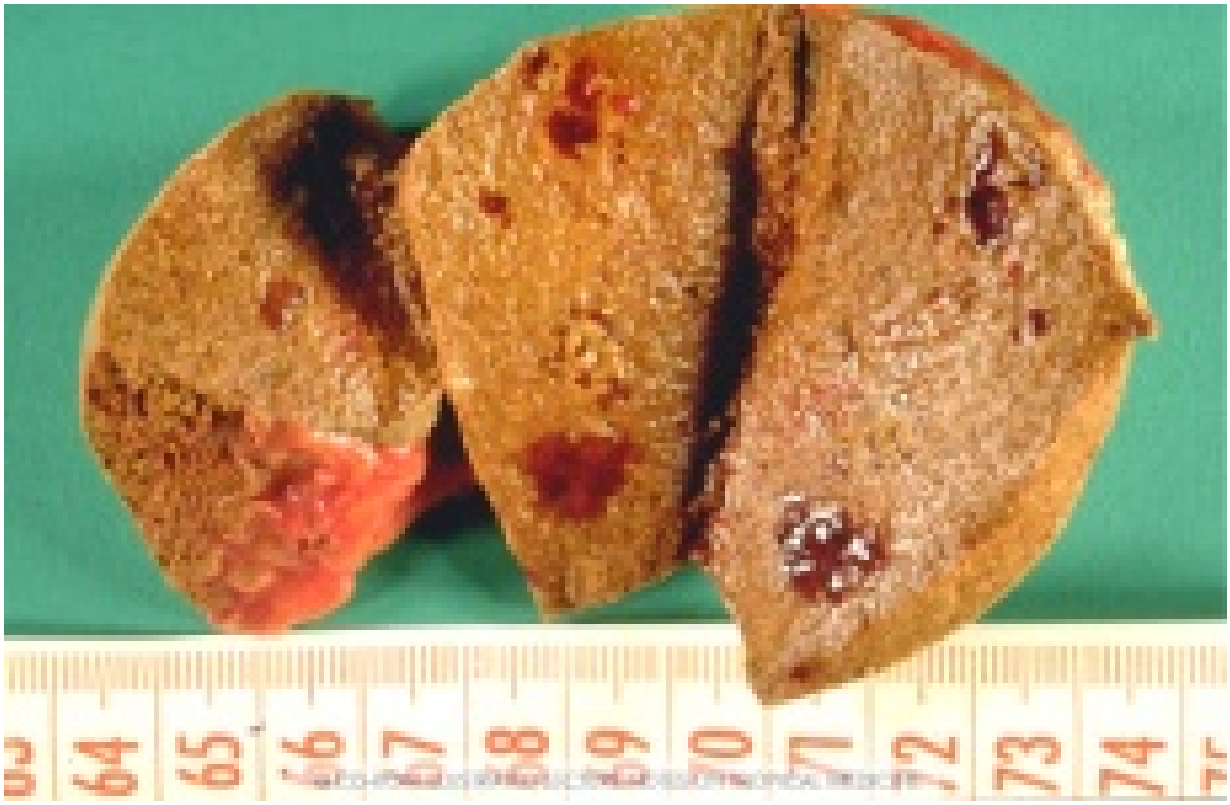
Due to kidney damage, patients with sickle cell anaemia usually have difficulty in concentrating their urine and are susceptible to dehydration. Hyposthenuria may become evident in childhood as enuresis.

Glomerular sclerosis, manifested by proteinuria, progresses as patients age. Chronic renal failure occurs in up to 5% of patients with sickle cell anaemia. Pulmonary infarctions contribute to acute chest syndrome, with pain, dyspnoea and a poor general condition. Small cerebral watershed infarcts may be clinically silent but produce cognitive defects shown by neuropsychiatric testing. Hemiplegia can result from cerebral infarction. Most patients with brain injury require long term transfusion therapy.

Eye problems

Occlusion of small retinal vessels with neovascularization is asymptomatic until haemorrhage occurs within the vitreous. Detachment of the retina, more common in late disease, is a feared complication, and an important cause of blindness, together with occlusion of the central retinal artery. The latter condition is a medical emergency, for which urgent transfusion is imperative.

Autosplenectomy



Splenic atrophy in sickle cell anaemia; photo Dr Van den Enden, ITM

Because of the repeated infarctions of the spleen, sickle cell anaemia patients over the age of 5 years no longer have a functioning spleen. Asplenic children are very susceptible to bacterial infections, including pneumococci (i.e. encapsulated bacteria, *Streptococcus pneumoniae*). Osteomyelitis caused by among others, *Salmonella* and staphylococci is common. Often it is difficult to distinguish between pulmonary infarction and pneumonia and between osteomyelitis and bone infarction.

Acute chest syndrome

This syndrome consists of a collection of problems, such as acute chest pain, dyspnoea, coughing, fever, hypoxemia, leukocytosis and pulmonary infiltrates, mainly in the inferior lobes. This can develop into a full-blown ARDS (Acute Respiratory Distress Syndrome). Bone marrow infarctions followed by fat and even bone marrow embolism play a part (beware of sickle patients with first pain in limbs, followed by chest problems). Atelectasis also

contributes and often develops as a result of hypoventilation that accompanies rib pain and the use of opiates. At autopsy in 75% of fatal cases bone spicules are found in the lung. In 60% of patients with acute chest syndrome, fat-loaded macrophages are found in the broncho-alveolar fluid. Because of the pain in the chest wall, patients are able to breathe less deeply (“splinting”) with hypoventilation, atelectasis and perhaps superinfection as a result. Hypoxemia increases the adhesion of red blood cells to the endothelium, via the increased expression of the adhesion molecule VCAM-1 on the endothelium. Breathing in regularly, as deeply as possible, is an important part of treatment (“incentive spirometry”). The patient is asked to breathe in deeply 10 times and to do this every two hours while awake. There is a clear role of opioids in promoting to control pain with careful monitoring to avoid over-sedation and hypoventilation. The administration of oxygen, antibiotics and standard or exchange transfusion completes the treatment. In a good hospital, the mortality of acute chest syndrome is 2% for children and 5% for adults.

Pulmonary hypertension

Pulmonary hypertension is a feared complication in chronic and severe haemolytic anaemias, such as thalassemia major, congenital spherocytosis and paroxysmal nocturnal haemoglobinuria. Pulmonary hypertension occurs in about one third of all patients with sickle cell disease. Asplenia increases the circulation of platelet-derived mediators, which promotes pulmonary microthromboses and adhesion of erythrocytes to the endothelium. Haemolysis results in the release of free haemoglobin, which scavenges nitric oxide, causing vasoconstriction.

Priapism

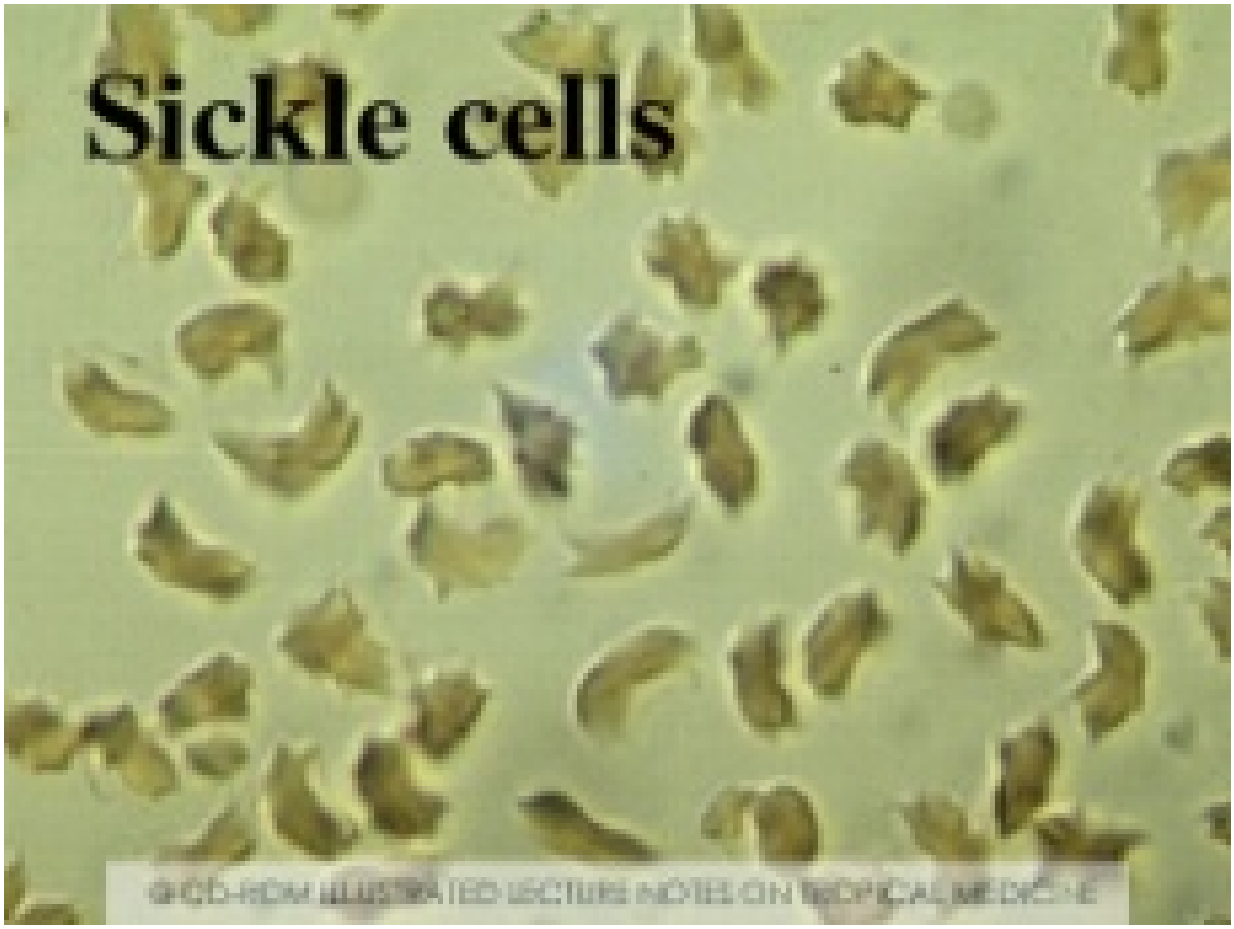
Priapism is a persistent and painful erection [Lat. priapus, God of procreation]. It is not associated with sexual stimulation. It is an important complication of sickle cell disease. By adulthood, 90% of males with sickle cell anaemia will have had a least one episode of priapism. The blood that flows into the corpora cavernosa of the penis has difficulty leaving the organ due to venous thrombosis. Because of acidification and hypoxia, sickling of red blood cells increases still further. If priapism persists longer than 4 hours, surgery is definitely required. Persistent priapism (>24 hours) results in fibrosis and impotence. As an initial

treatment the patient can be made to go up and down stairs in order to divert blood flow to the leg muscles (the “steal mechanism” principle) or have external compression of the perineum applied, perhaps with ice. General measures such as hydration, (exchange) transfusion and analgesics are necessary. Aspiration and irrigation of the corpus cavernosum with or without saline irrigation is necessary in an episode of priapism lasting more than four hours. The alpha-adrenergic agonist phenylephrine can be injected in the corpora cavernosa, causing blood to leave the corpora cavernosa due to smooth muscle contraction in the penile arteries.

Diagnosis

Laboratory

A sickling test can be carried out in field laboratories (Emmel’s test). In this, a drop of blood is placed on a glass slide. This is covered with a coverslip and the edges are sealed with some vaseline (to prevent contact with the air). As time goes by and the oxygen in the blood falls further (due to the metabolism of the cells) the red blood cells will sickle. This test can be accelerated by adding a drop of sodium metabisulphite to the blood.



Red blood cells of a homozygote sickle cell anaemia patient undergo dramatic change in shape when oxygen is excluded from their environment (Emmel test). Copyright ITM

Heterozygotes

Since normal and mutated beta chains are produced equally rapidly, it may be expected that heterozygotes would have ±50% Hb S and ±50% of Hb A. However, because alpha chains bind more easily to the normal beta chains than the mutated forms, there is a relative excess of mutated beta chains in the tetramers. The excess mutated chains are then destroyed. As a result, most heterozygotes have about 35% Hb S rather than 50%, and about 65% Hb A. The diagnosis of sickle cell trait is established by haemoglobin electrophoresis. If a non-transfused patient with sickle cell disease would have e.g. 65% HbS and about 30% HbA, especially if Hb A2 would be elevated, the suspicion of Hb S/beta^{+}thalassemia would be strong.

Homozygotes

There is severe anaemia (usually Hb 6-9 g%) with considerable reticulocytosis. A blood smear of a homozygote shows many sickle cells, in contrast to that of a heterozygote. The diagnosis can be confirmed by haemoglobin electrophoresis. On electrophoresis it can be seen that most of the haemoglobin consists of Hb S (often more than 80%); the remainder consists of Hb F and Hb A2. Of course, no Hb A can be found. There is often thrombocytosis and leucocytosis.

Treatment

General

Apart from bone marrow transplantation, there is no curative therapy. Hematopoietic stem cell therapy and gene therapy remain possibilities for the future. The suffering of children can be reduced.

It is possible to stimulate the induction of haemoglobin F by medication. In contrast with haemoglobin A2 (alpha2 delta2), a minor haemoglobin which is uniformly distributed in all adult red cells, haemoglobin F is found (in normal people) in 0,2 to 7 percent of the adult red cells, and in those cells, it constitutes 14 to 28 percent of the total haemoglobin. They are called “F”cells. Hb F contains gamma chains instead of beta chains (structure alpha2 gamma2). Hb F has a greater affinity for oxygen than Hb A. This helps the fetus to draw oxygen from the mother’s blood. Hb F inhibits the polymerization of deoxy-Hb S. This inhibits the sickling of red blood cells. After birth, the neonate still has more than 50% Hb F in his blood.

This explains why very young children are free of sickling crises. After birth the genes for the gamma chains are less active because they become methylated. This is reversible however.

Hydroxyurea is a mainstay in the treatment of sickle cell anaemia. Hydroxyurea (Hydrea®) is a cytostatic drug which was long used in patients with polycythemia vera or chronic myeloid leukaemia, to counter hyperleukocytosis. Another important effect of hydroxyurea is

production of nitric oxide (NO), a vasodilator. The anti-sickling activity results from induction of haemoglobin F through activation of a specific promoter for the haemoglobin gamma-chain gene. There is also a reduced expression of adhesion molecules (e.g. VCAM-1, L-selectin), as a result of which red blood cells and neutrophils adhere less easily to the vascular endothelium. Hydroxyurea can be used in prevention (not in an acute crisis). Hydroxyurea reduces the frequency and the severity of the attacks (up to 40% decrease in mortality).

Maintenance treatment

1. **Folic acid.** The patients have a greater need for this vitamin due to the high demands of the red bone marrow. It is important to check vitamin B12 status, in order not to mask a cyanocobalamin deficiency.
2. **Penicillin prophylaxis** is given to reduce the number of infectious episodes. Today vaccination with **pneumococcal vaccine** lessens the importance, but porphylactic penicillin is still recommended to all children with sickle cell diseases till the age of 5 years.Penicillin V 125 mg orally twice daily till the age of 3 years is increased to 250 mg twice daily until the age of 5.
3. **Zinc.** Up to 20% of sickle cell anaemia patients have persistent leg wounds. Many patients tend to be zinc deficient, possible via excessive renal excretion due renal damage secondary to repeated infarctions in the hypertonic renal medulla. Zinc is a trace element needed for certain enzymes, including some metalloproteases which are important in wound healing. Zinc deficiency makes wounds heal more slowly. Zinc sulphate or zinc acetate per mouth (e.g. 30 mg per day) can help here, but is often given as part of multivitamin supplements (without iron). It is important to mention that prolonged treatment with hydroxyurea can lead to slower healing of leg ulcers.

Additional important measures

1. **Immunizations** are a cornerstone to prevent infections in sickle cell disease: routine childhood vaccinations are recommended including vaccination against *Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae B* and hepatitis B. Yearly influenza vaccination is advised.
2. **Antibiotics.** Every patient must have at home a stand-by broad-spectrum antibiotic such

as co-amoxiclav. Azitromycin can be used in case of penicillin-allergy. They should take this at the first signs of infection. The reason for having the antibiotic at home is that patients often live a long way from a hospital and might lose lots of precious time before they are seen by a medical doctor.

3. **Malaria prevention** is absolutely indicated in an endemic area as infection with this parasite can be fatal.
4. **Preventive transfusions** are a double-edged sword and are not given routinely. With transfusions the haemoglobin level can be kept at a higher level, which reduces the consequences of anaemia. This also reduces the concentration of Hb S in the blood, thus reducing the risk of complications. However repeated transfusions gradually cause severe transfusion reactions. It is best always to give blood that is low in leukocytes. Since in the long term there will be sensitization to the minor blood groups, the red blood cells in later transfusions will be destroyed very quickly. Slow iron poisoning also occurs, damaging the heart, the liver and some endocrine organs (pancreas, testis). Iron chelation therapy is indicated. In the case of acute aplastic crisis (triggered by infection with parvovirus B19) and splenic sequestration crisis, transfusions are essential. They are also important in acute chest syndrome. Exchange transfusions are also a therapeutic option.

Hydroxyurea (= hydroxycarbamide, Hydrea®). Usually 500 mg three times daily is given in order to raise the level of haemoglobin F to above 15%. Regular checking of the number of white blood cells is indicated (it is a cytostatic drug). Another side-effect is slower healing of leg ulcers. Pregnancy is a contra-indication. Since the introduction of hydroxyurea in treatment, the quality of life for many patients has improved dramatically. Since the drug is cheap, it is not outside the means of many third-world families and hospitals.

Heredity should be explained to the parents so that they have the correct information in order to decide whether or not to have another child. If both parents are carriers, the probability of a normal child (Hb A) is 25%, the probability of a healthy heterozygous child is 50% and the probability of a homozygous Hb S child is 25%.

Management of ARDS in sickle cell crisis

The mainstay of treatment for patients with ARDS is supportive care and mechanical

ventilation.

Although the ventilator can be lifesaving, it can be a source of further lung injury. A crucial intervention in the acute chest syndrome is reduction of the percentage of haemoglobin S in the patient's blood. One can use "normal" transfusions, but this also increases blood volume and viscosity. Red-cell exchange transfusion avoids this complication. The aim is to reduce the percentage haemoglobin S to well below 30%. The final (desperate) measure is the use of extracorporeal membrane oxygenation (ECMO).

What should be done in the event of a sickle cell crisis?

Antibiotics, transfusions (normal or exchange transfusion), oxygen, pain control with paracetamol-codeine, ibuprofen or morphine analogues are all part of sickle cell crisis management. Sufficient fluid should be administered because the kidneys have difficulty in producing concentrated urine. Often 3 to 4 litres a day are given (adults) if possible orally, otherwise IV. Severe acidosis is best corrected quickly with bicarbonate, although no spectacular results can be expected. In the case of rib or tissue infarctions, and also in chest disorders, it is important that the patient is urged to breathe deeply (10 maximum inspirations) at regular intervals e.g. every two hours. This prevents atelectasis. The polymerizing of Hb S is promoted strongly by dehydration. The higher the salt concentration in the blood, the more quickly the cells sickle. Patients with a sickle cell crisis often have a hypercoagulable state, thus thromboembolism prophylaxis is essential during hospitalization. This can be done with LMWH's or unfractionated heparin.

What happens if an operation is carried out?

Many homozygous sickle cell patients have to undergo surgery due to complications of their illness (mainly cholecystectomy or orthopaedic surgery) or for other reasons. Perioperative complications are common in patients with sickle cell anaemia. During anaesthesia, the operation itself and in the post-operative phase hypoxia must be avoided. Perioperative hypoxia, tissue hypoperfusion and acidosis can trigger vaso-occlusive crises and cause organ dysfunction (mainly acute chest syndrome and pain crises). Pre-operatively (exchange-)transfusion can be given.

Pregnancy and prenatal care

Pregnant homozygous sickle cell anaemia patients are rare in Africa. In the absence of medical care, mortality for mother and neonate can be as high as 20% and 50% respectively. The most common complications during pregnancy for women with sickle cell disease are hypertension and preeclampsia (14%). It has been suggested that maternal anaemia and placental ischemia may play a role, as slow placental circulation and a high degree of oxygen-extraction promote sickling. A high percentage of the pregnancies result in preterm deliveries (27%) and infants small for gestational age (21%). It is best to keep the mother's haemoglobin level above 10 gram %, although there is controversy about the use of prophylactic transfusions. It seems logical to reserve transfusions for complications, rather than use them routinely. Hydroxyurea is contra-indicated in pregnancy as it is teratogenic. However, in a small number of cases where hydroxyurea was taken throughout pregnancy, no fetal malformations occurred. During labour and delivery the mother should receive oxygen and should be well hydrated.

Bone marrow transplantation

For patients with severe symptoms, especially severe neurological symptoms or complications, an argument could be made for early bone marrow transplantation if a HLA-identical sibling donor were available. The principal complication of allogeneic stem-cell transplantation (the transplantation of grafts from genetically different donors) is graft-versus-host disease (GVHD), which can occur despite aggressive immunosuppressive prophylaxis, even when the donor is a so-called "perfectly matched" (syn. HLA-identical) sibling. The few patients, mostly children, with sickle cell disease who have undergone bone marrow transplantation after a myeloablative conditioning regimen have become asymptomatic despite incomplete replacement of their marrow with donor cells (mixed chimerism).

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