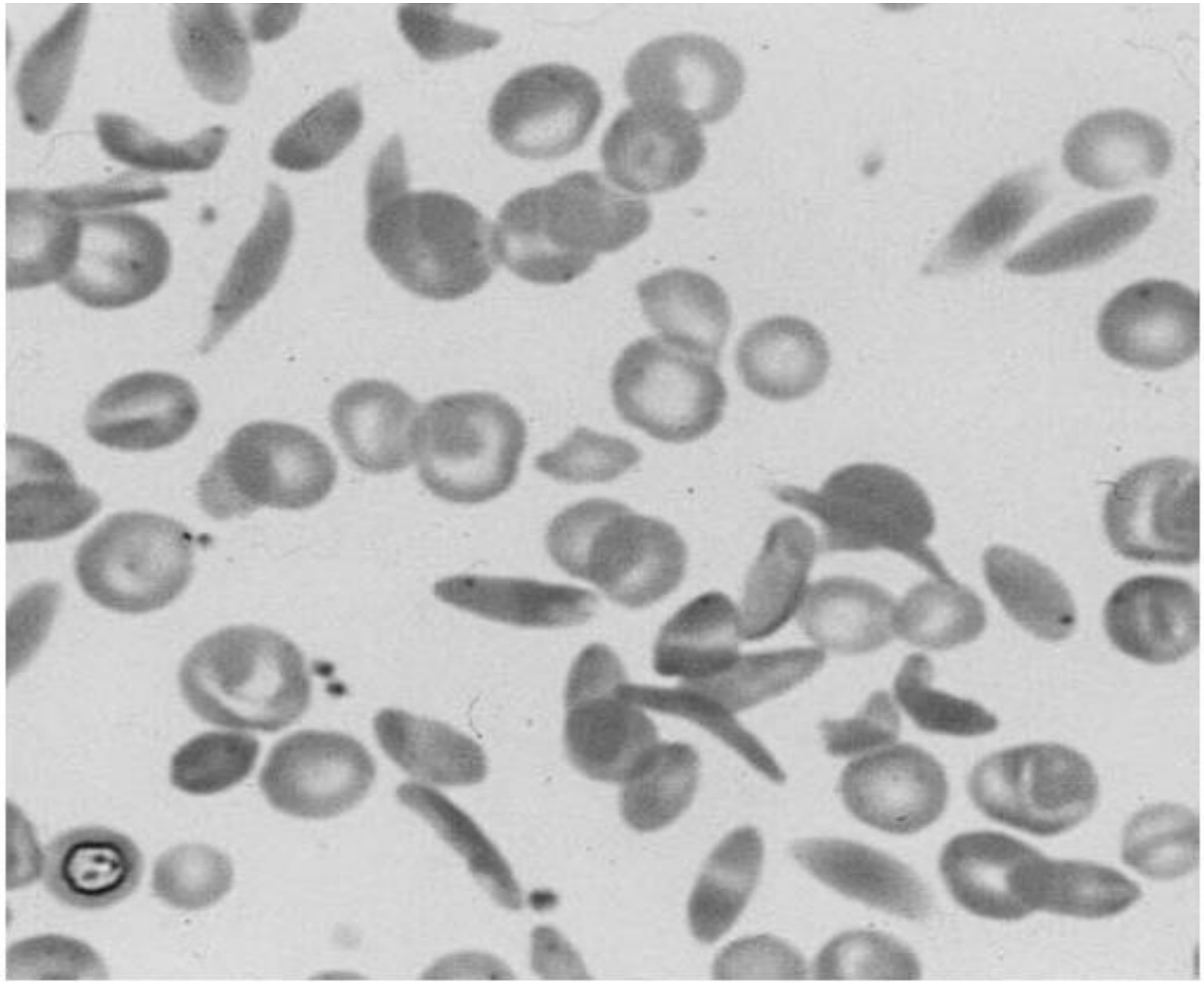
SICKLE CELL DISEASE

DEFINITION

Sickle cell disease, caused by a mutation in the β-globin gene (HBB), consists of a group of chronic hemolytic anemias, all characterized by vaso-occlusive events, hemolytic anemia, vasculopathy, widespread acute and chronic organ damage, and premature mortality.



EPIDEMIOLOGY

The prevalences of the various forms of sickle cell disease and of the sickle cell trait (HbAS), which is not truly a form of sickle cell disease,. The sickle hemoglobin mutation became prominent in equatorial Africa, the Middle East, and India several thousand years ago, when deforestation, the rise of agriculture, and stagnant pooling of water permitted Plasmodium falciparum infection to become endemic. Individuals with HbAS were more likely to survive to reproductive age and had a selective advantage where falciparum malaria was present. Slave trading and war spread this mutation from Africa and other sites of origin to the Americas, throughout the Mediterranean basin, and eastward to the Indian subcontinent. In some sites in Africa, half the population has HbAS. The partial protection provided from severe malaria by HbAS, HbC, HbE, α-thalassemia, and β-thalassemia along with other red blood cell traits is the source of the selective pressure maintaining the high prevalence of these carrier states.

- PATHOBIOLOGY

Globin, the protein portion of hemoglobin, harbors the iron-containing porphyrin heme ring and permits the molecule to operate efficiently in oxygen transport and its other physiologic functions. Mutations can alter the primary amino acid sequence of the globin polypeptide, sometimes resulting in clinically significant diseases called hemoglobinopathies, of which sickle cell disease is an example. Sickle hemoglobin (HbS: $\alpha 2\beta 2S$) is caused by an adenine (A) to thymidine (T) substitution (GAG → GTG) in codon 6 of the β-globin gene (HBB), resulting in replacement of the normal glutamic acid residue by a valine (Glu6Val). HbS polymerizes when it is deoxygenated, a property only of hemoglobin variants that have the HBB Glu6Val substitution. Critical amounts of HbS polymer within sickle erythrocytes cause cellular injury and lead to the phenotype of sickle cell disease, which is recognized by hemolytic anemia and vaso-occlusion. Other hemoglobin variants, such as HbE and HbC, are also common.

Clinical features

• Highly variable. Many have few symptoms whilst others have severe and frequent crises, marked haemolytic anaemia, and chronic organ damage. HbF level plays role in ameliorating symptoms (iHbF l fewer and milder crises). Likely impact of inherited and environmental factors. Spectrum of haemolytic and vasoocclusive phenotype.

• Newborns—have higher HbF level than normal adult, protected during fi rst 8–20 weeks of life. Symptoms start when HbF level falls.

• Infection—high morbidity and mortality due to bacterial and viral infection due to functional hyposplenism. Pneumococcal septicaemia (Streptococcus pneumoniae) well recognized. Other infecting organisms: meningococcus (Neisseria meningitidis), Escherichia coli, and Haemophilus influenzae (hyposplenic). i malaria risk with higher complication rate (prophylaxis encouraged)
• Steady state anaemia—children and adults often severely anaemic (Hb 76.0–9.0 g/dL). The steady state Hb of each patient should be noted at the annual review. Anaemia is chronic (haemolytic) and patients generally well-adapted until episode of decompensation (e.g. severe infection) occurs. Causes of actue-on-chronic anaemia include

increase haemolysis (usually 1–2g/dL) due to infection including malaria, vaso-occlusive crisis, transfusion reaction. G6PD deficiency can contribute to increase haemolysis. Sequestration syndromes including acute chest syndrome, splenic and hepatic sequestration and acute aplasia usually due to parvovirus B19 infection. Apart from aplastic crisis all others should be accompanied by increase reticulocyte count. In some cases transfusion therapy can be life saving but decision to transfuse should be made following discussion with an experienced clinician.

Acute and chronic sickle complications

- Vaso-occlusive crisis: presents with severe bone, joint, and muscle pain. Bone pain affects long bones and spine, and is due to occlusion of small vessels. Triggers: infection, dehydration, alcohol, menstruation, cold, and temperature changes—often identifiable precipitant found. Dactylitis is a subform mainly children age <6 years. Metacarpals, metatarsals, backs of hands and feet become swollen and tender (small vessel occlusion and infarction). Recurrent, can result in permanent radiological abnormalities in bones of the hands and feet (rare) with digit shortening.
- Sepsis: fever without source, commence broad-spectrum antibiotics without delay and organize septic screen.
- Pulmonary complications: acute chest syndrome—common cause of death, seen in 40% of patients, children > adults (more severe in adults). Chest wall pain, sometimes with pleurisy, fever, and SOB. Resembles infection, infarction, or embolism. May follow simple pain crisis and common postoperatively. Early recognition important. Requires prompt and vigorous treatment. Transfer to ITU if pO2 cannot be kept >70mmHg on air. Consider CPAP. Treat infection vigorously, cover for S. pneumoniae, H. influenzae, Mycoplasma, Legionella. Exchange transfusion can be life saving. Pulmonary hypertension recognized chronic complication. Screening ECHO recommended. TRV max. jet velocity >2.5m/s associated with increase risk of death. Chronic lung disease also seen, restrictive defect on PFT.

• Sequestration crises—mainly children (30%). Pooling of large volumes of blood in spleen and/or liver. Severe hypotension and profound anaemia may result in death. Splenic sequestration is seen predominantly in children <6 years of age; often occurs following a viral infection.

• Abdominal pain and hepatobilary complications: gallstones common due to chronic haemolysis. RUQ pain may represent biliary colic, cholangitis, sickle chronic hepatopathy. Laparoscopic cholecystectomy may help prevent recurrent acute biliary complications.

• Neurological complications: silent infarcts common due to small vessel vasculopathy. Increase risk of ischaemic stroke (young children > adults but increases in older adults). Haemorrhagic stroke more common in young adults. Significant cause of death. Cognitive deficits recognized in children and adults. TCD screening recommended for children from age 2 with transfusion therapy for 1° stroke prevention. Acute stroke should be managed with exchange transfusion

- Eye complications: proliferative retinopathy (in 30%; more common in SC disease, affecting 75% adults), blindness (esp. HbSC), retinal artery occlusion, retinal detachment. Refer to ophthalmology if sudden-onset visual impairment, eye trauma.
- Renal and genitourinary:

haematuria common, likely due to medullary sickling. Frank haematuria—acute papillary necrosis. Renal reserve is impaired. Risk of acute kidney injury. Risk factors for chronic sickle nephropathy: hypertension, proteinuria, severe anaemia, haematuria. Avoid NSAIDs, start ACE inhibitor, good BP control. Postrenal transplant exchange transfusion recommended. Hyposthenuria (inability to concentrate urine) common cause of nocturnal enuresis. Priapism common (40%) men. Form of compartment syndrome so fulminant (>4h) priapism is medical emergency. Give oral alpha agonist, urgent penile aspiration, washout, and intracorporal alpha agonist injection (urology).

Other problems

- Growth retardation: common in children, but adult may have normal height (weight tends to be lower than normal). Sexual maturation delayed.
- Acute fat embolism syndrome: bone marrow infarction and necrosis with embolization of fat droplets. Triggers acute systemic illness. Progressive anaemia, thrombocytopenia, DIC, reticulocytopenia. Can lead to multiorgan failure.
- Locomotor: avascular necrosis of the head of the femur or humerus, arthritis, and osteomyelitis (Salmonella infection).
- Chronic leg ulceration is a complication of many haemoglobinopathies including sickle cell anaemia. Ischaemia is main cause. Rare in SC disease.
- CVS: murmurs (anaemia), tachycardia.
- Psychosocial: depression, socially withdrawn. Anaesthesia and surgery
- A benefit from preoperative transfusion in patients with HbSS/HbS/β thalassaemia having low/medium-risk procedures (e.g. adenotonsillectomies, lap chlocystectomies). All patients should have IV hydration the evening prior to procedure under GA. Attention should be paid to oxygenation, hydration, and temperature control pre/peri- and postoperatively. Early mobilization, incentive spirometry, and VTE prophylaxis should be considered. Obstetric care
- Pregnant patients should be managed by team of experienced haematologists/obstetricians.
- Continue penicillin/folic acid. Add aspirin from 12 weeks' gestation. Stop NSAIDs. Prophylactic LMWH should be considered during antenatal admissions/post delivery. No evidence for routine transfusions.

Laboratory features

Anaemia usual (Hb 7.0–9.0g/dL in HbSS although may be much lower; HbSC have higher Hb). Reticulocytes may be increased (to 10–20%) reflecting intense BM production of RBCs. Anaemic symptoms usually mild since HbS has reduced O2 affinity with O2 dissociation curve shifted to the right. MCV and MCH are normal, unless also thalassaemia trait (25% cases). Blood film shows marked variation in red cell size with prominent sickle cells and target cells; basophilic stippling, Howell–Jolly bodies, and Pappenheimer bodies (hyposplenic features after infancy). Sickle solubility test (e.g. sodium dithionate) will be positive. Does not discriminate between sickle cell trait and homozygous disease. Serum bilirubin often increased (due to excess red cell breakdown).

Confi rmatory tests Hb electrophoresis or HPLC shows 80–99% HbS with no normal HbA. HbF may be elevated to about 15%. Parents will have features of sickle cell trait. Laboratory screening tests Acceptable tests include high-performance liquid chromatography (HPLC), generally used as 1st-line screening as less labour intensive and cost effective. Also quantitates HbS %. Isoelectric focusing (IEF), capillary electrophoresis (CE), and cellulose acetate electrophoresis (CAE)

Antenatal screening

Pregnant women should be offered screening as part of their antenatal care in early pregnancy. The family origins questionnaire should be used for low-prevalence regions. If both parents of fetus are carriers offer prenatal/neonatal diagnosis. Prenatal diagnosis May be carried out from 1st trimester (chorionic villus sampling from 10 weeks' gestation) or 2nd trimester (fetal blood sampling from umbilical cord or trophoblast DNA from amniotic fl uid).

Management—general

- Health maintenance: avoid dehydration, extremes of temperature, over exertion. Compliance with penicillin prophylaxis (current UK guidelines recommend lifelong), folate replacement. Pneumococcal vaccination, screening for complications—transcranial Doppler (TCD) age 2–16, urinalysis for proteinuria, ECHO for pulmonary hypertension (TRV jet velocity >2.5m/s). Education around analgesic use, life style adaptation. At least annual review in specialist clinic.
- Acute and chronic pain management: most patients with sickle cell disease suff er painful crises. Chronic pain increases with age. May be clear precipitant of acute pain— infection, temperature changes (hot or cold), or stress. Chronic pain requires multidisciplinary team input (pain specialists, psychology).
- Fluid replacement—good daily hydration. During acute crisis IV maybe required. Hyperhydration should be avoided.
- Management of pain crisis.

Management of painful crises

- Regular parenteral opiates are useful initially but should be tapered and replaced with oral analgesia.
- Red cell transfusion is generally not required although is indicated in sudden anaemia in children (e.g. splenic sequestration), parvovirus B19 infection (with associated transient red cell aplasia), or acute chest syndrome (hypoxia).

Other problems

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• Psychosocial: depression, socially withdrawn.

Anaesthesia and surgery

• Data from the TAPS trial demonstrated a benefit from preoperative transfusion in patients with HbSS/HbS/β thalassaemia having low/medium-risk procedures (e.g. adenotonsillectomies, lap chlocystectomies). All patients should have IV hydration the evening prior to procedure under GA. Attention should be paid to oxygenation, hydration, and temperature control pre/peri- and postoperatively. Early mobilization, incentive spirometry, and VTE prophylaxis should be considered. Obstetric care

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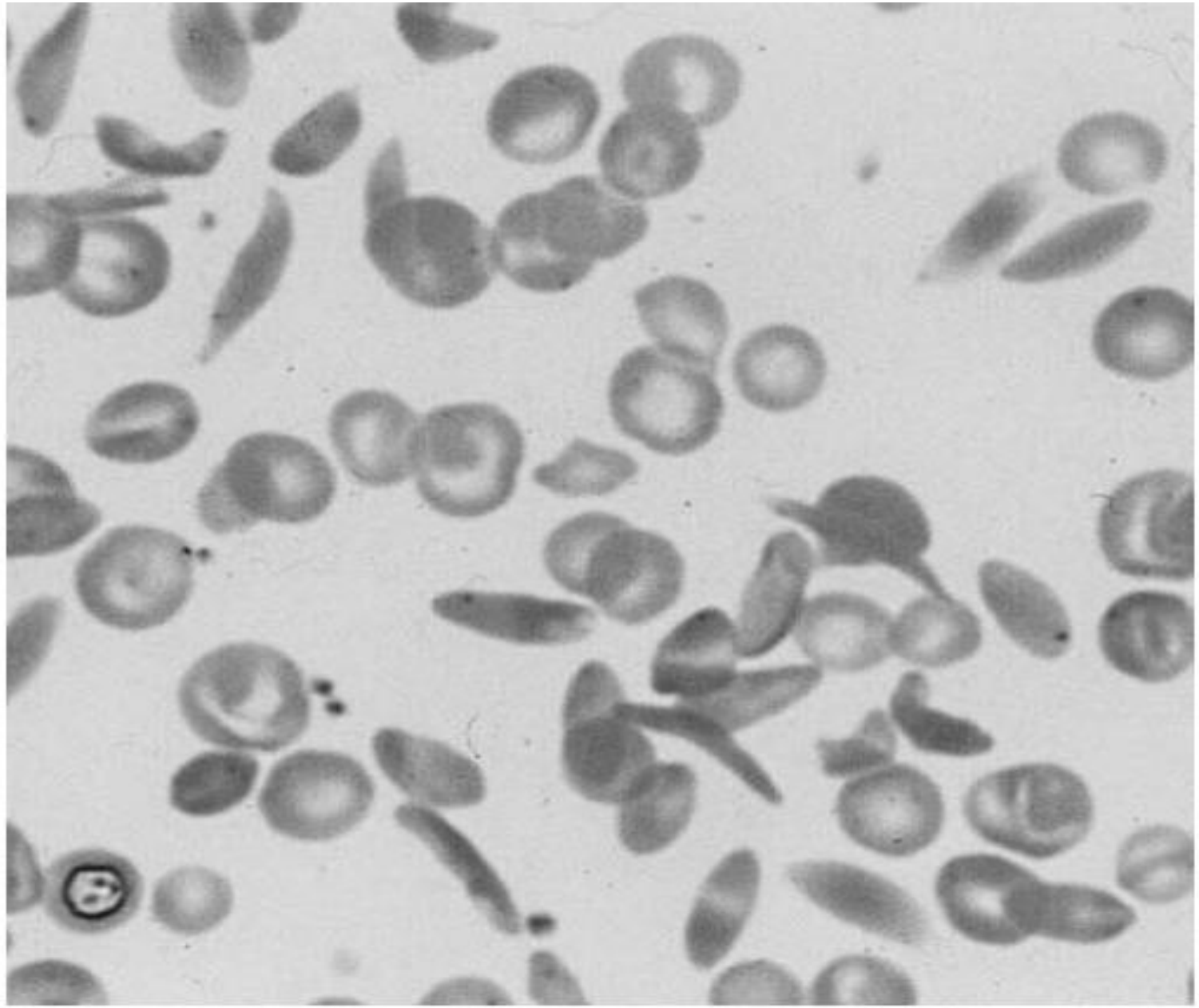

Confirmatory tests

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at alkaline pH can be used for screening or confirmation. Sickle solubility can be used as confirmation. Also examine the blood film.

Antenatal screening Pregnant women should be offered screening as part of their antenatal care in early pregnancy. The family origins questionnaire should be used for low-prevalence regions. If both parents of fetus are carriers offer prenatal/neonatal diagnosis.

Prenatal diagnosis

May be carried out from 1st trimester (chorionic villus sampling from 10 weeks' gestation) or 2nd trimester (fetal blood sampling from umbilical cord or trophoblast DNA from amniotic fluid).

DNA may be analysed using restriction enzyme digestion with Mst II and Southern blotting, RFLP analysis assessing both parental and fetal DNA haplotypes, oligonucleotide probes specific for sickle globin point mutation, or PCR amplification followed by restriction enzyme digestion of amplified DNA. ARMS (amplification refractory mutation system) PCR is useful in ambiguous cases. In late pregnancy fetal blood sampling may be used to confirm diagnosis. Newborn screening programme Detects infants in the neonatal period to allow early intervention with penicillin prophylaxis, initiation of parental education and awareness. Dry blood spots used with HPLC or IEF. As well as the routine childhood vaccinations additional pneumococcal vaccination (prevenar + pneumovax) recommended and timely hepatitis B and annual influenza vaccination.

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