Haematological Problems

9

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Contents

9.1 Haematological Basic Science

9.1.1 Blood Formation (Haematopoiesis)

The bone marrow is a mesenchymal derived tissue divided into irregular interconnective spaces by bone trabeculae. It consists of a complex haematopoietic cellular component that is extremely labile and continuously goes through self-replication and differentiation processes. These cells are supported by a micro environment composed of stromal cells (endothelial cells, fibroblast like cells, adipocytes), extracellular matrix and vascular structures.

- Embryonic haematopoeisis (which predominantly is associated with red cell development) begins in the yolk sac at the end of the 3rd week of gestation and declines to an insignificant level by the end of the first trimester.
- By the end of the first trimester, the liver is the dominant source of haematopoiesis producing all the haemopoietic elements. Hepatic haematopoietic activity reaches its maximum level at around the 3rd month and gradually declines from the 7th month until birth.
- Bone marrow haematopoiesis begins to occur at around the 5th month of gestation and continues to increase thereafter.
- Every day, in normal adult bone marrow, approximately 2.5 billion red cells, 1 billion granulocytes and 2.5 billion platelets are produced per kilogram of body weight.
- Haematopoiesis is regulated and sustained by a complex cellular interaction of haemopoietic and stromal elements and a network of cytokine growth factors including the interleukins and colony stimulating factors.

P. Puri and M. Höllwarth (eds.), *Pediatric Surgery: Diagnosis and Management,*
DOI: 10.1007/978-3-540-69560-8_9, © Springer-Verlag Berlin Heidelberg 2009

- All the cells of the haemopoietic system originate from a pluripotent haemopoietic stem cell (HSC). HSCs have the intrinsic capacity for self renewal and are low in number and divide infrequently. The committed progenitors are responsible for the massive amount of cell proliferation required to maintain blood cell production in numbers outlined above. The common lymphoid progenitors develop into T and B cells whereas the common myeloid progenitor gives rise to erythrocytes, megakaryocytes, monocytes and granulocytes.

9.1.2 Mechanisms of Haemostasis

Normal blood coagulation or haemostasis is a complex sequence of inter-related events by which the body prevents blood loss from the vascular tree. This is achieved by a multi-pathway interactive system with multiple negative and positive feedback loops, which ultimately ensure that blood is at all times fluid within the vasculature, but it also needs to be transformed into a clot when there is a breach in the integrity of the vascular tree. The protein (pro- and anticoagulants—outlined below) and cellular (endothelial cells, monocytes and platelets) components have also shown to be intimately involved in the inflammatory response, vasculogenesis, metastasis, cellular proliferation and tissue repair.

- Tissue factor, a cell surface glycoprotein is the principal biological initiator of blood coagulation.
- Exposure of circulating plasma VIIa to tissue factor triggers the coagulation cascade *in vivo*, which results in thrombin generation (Fig. 9.1).
- Thrombin converts soluble fibrinogen to a fibrin network, activates platelets and stimulates coagulation by positive feedback activators of cofactors, factors V and VIII and the zymogens II, VII, IX, X, XII and XIII.
- Under physiological conditions, pro-and anticoagulant (see below) mechanisms are balanced in favour of anticoagulation; however, at sites of vascular damage resulting from inflammation, trauma, etc, the anticoagulant system is down-regulated and thus procoagulant forces prevail.

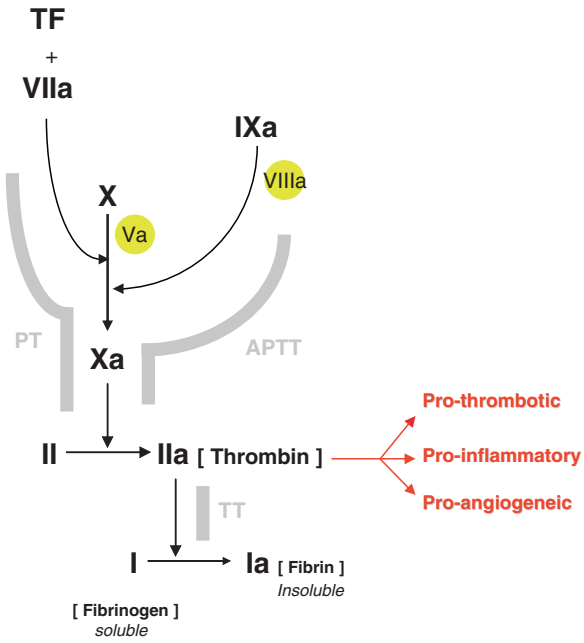

Fig. 9.1 Blood coagulation is initiated (initiation phase) when tissue factor (TF), expressed after injury to cell (endothelial, monocytic cells, etc.) wall, is exposed to FVIIa in the bloodstream. TF-FVIIa complex in turn activates FIX to FIXa and FX to FXa. FIXa with its cofactor FVIIIa in turn also activates FX to FXa (amplication phase). FXa with its cofactor FVa activates Prothrombin (II) to Thrombin (IIa) (propagation phase). Thrombin converts soluble fibrinogen to insoluble fibrin. Thrombin is not only prothrombotic but activates platelets and is proinflammatory and promotes new vessel formation. Shown in grey are three global coagulation screens prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT)

9.1.3 Natural Anticoagulation Control Mechanisms

Several natural anticoagulant mechanisms have been discovered that exert dampening effects upon procoagulation and in turn halt the generation of thrombin. The major anticoagulant inhibitors of blood coagulation include tissue pathway inhibitor, antithrombin and the Protein C pathway (Fig. 9.2). The protein C pathway regulates the amount of thrombin in the microcirculation whereas the tissue factor pathway inhibitor and the antithrombin exert more of an effect in the macro-circulation.

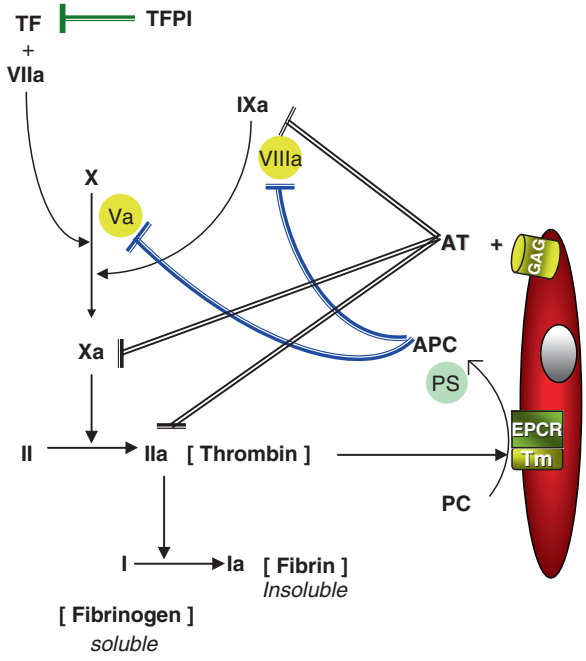

Fig. 9.2 The initiation phase of coagulation is controlled by inhibiting the complex of TF, FVIIa and FXa by tissue factor pathway inhibitor (TFPI). The amplification phase of coagulation is blocked by the protein C pathway. Protein C (PC) is activated by a complex of thrombin, thrombomodulin (Tm), and endothelial protein C receptor (EPCR) to APC which in association with protein S (PS) inactivates FVa and FVIIa. The thrombin formed in the propagation phase is controlled by antithrombin (AT)

9.1.4 Platelets

Platelets derived from megakaryocytes play an essenial role in thrombosis and haemostasis. Megarkaryopoiesis in the bone marrow is governed by a complex interaction of cytokines (e.g. thrombopoietin) and their receptors (e.g. c-mpl). Platelets play a major role in primary haemostasis (adhesion, aggregation and release). Platelets may also have functional defects and these can manifest as a diminished platelet response to weak agonists (storage pool defects and release defects or aspirin-like syndromes) (Table 9.1) or where there is an absence of platelet aggregation to all agonists as seen in Glanzmann's thrombasthenia, dysfibrinogenaemia or afibrinogenaemia. These disorders cause primary haemostatic bleeding ranging from mild to severe.

Table 9.1 Platelet function disorders

- Storage Pool Disorders (SPD)
  - Dense granule storage pool disease (δ-SPD)
    - Hermanksy-Pudlak
    - Chediak-Higashi
    - Wiskott-Aldrich
    - Thrombocytopenia absent radii
    - May-Hegglin
  - Alpha granule storage pool disease (α-SPD)
    - Grey platelet syndrome
  - δ, α storage pool disease (δ,α-SPD)
- Release defects
  - Asprin-like syndromes
    - Cyclooxygenase deficiency
    - Thromboxane synthetase deficiency
    - Thromboxane A2 receptor defects
  - Drug-induced
    - Asprin
    - Other non-steroidal anti-inflammatory agents
    - Furosemide
    - Nitrofurantoin

9.1.5 Blood Groups and Antibodies

There are 26 blood group systems corresponding to red blood cell (RBC) surface antigens. The ABO system is the most important. Antibodies against blood group antigens A and B occur naturally in people who lack these antigens, for example, patients who are Group A will have naturally occurring anti-B antibodies, while patients who are Group O will have anti-A and anti-B and so on. These antibodies are IgM, and so can cause complement activation and acute intravascular haemolysis. Other clinically important antibodies do not occur naturally and require exposure to an antigen—either by a blood product transfusion or *via* feto-maternal exposure. These antigens vary in their immunogenicity, e.g. the Rhesus antigen "D" and the Kell antigen are highly immunogenic.

9.2 Secelted Haemato-Surgical Case Scenarios

9.2.1 Haemophilia

Haemophilia A (factor VIII deficiency) is the second commonest inherited bleeding disorder with a frequency of approximately 1 in 500 male births. Haemophilia B

(factor IX Deficiency) is approximately one-sixth as common as Haemophilia A.

Clinical Features

- Majority of severe and moderate (factor VIII levels <1% and 1–5%, respectively) cases present in the first few years of life.
- Haemophilia A and B are X-linked recessive disorders.
- One-third of cases of FVIII Deficiency have no family history (spontaneous mutations).
- When there is no family history, infants with moderate or severe disease usually present:
  - Post-circumcision bleeding (Fig. 9.3)
  - Bad "toddler bruising"
  - Soft tissue and muscle or joint bleeds at 6–18 months of age
  - Intracranial ilio-psoas, intra-abdominal haematuria are all rare
- Children presenting with bruising and severe bleeding, not uncommon for the first presumed diagnosis to be non-accidental injury.
- True coagulation defects need to be excluded. Normal coagulation screen does not exclude all significant coagulation disorders

Treatment

- Objectives of modern management include the following:
  - Prevention of chronic joint damage (Fig. 9.4)
  - Prevention of "life threatening" bleeds
  - To facilitate social and physical well-being and help children achieve their full potential
  - To provide a comprehensive service to the family
- Successful treatment involves prompt and sufficient intravenous replacement of FVIII/FIX to haemostatic levels.
- Prophylactic administration of factor concentrate converts a child who has severe or moderately severe disease to a child with mild disease. Because of the different plasma half-lives of coagulation factors, FVIII is given three times per week and FIX is given twice a week in prophylactic programmes.
- Prophylaxis usually requires a central venous access device (see below) to be placed in the child to facilitate regular intravenous administration.

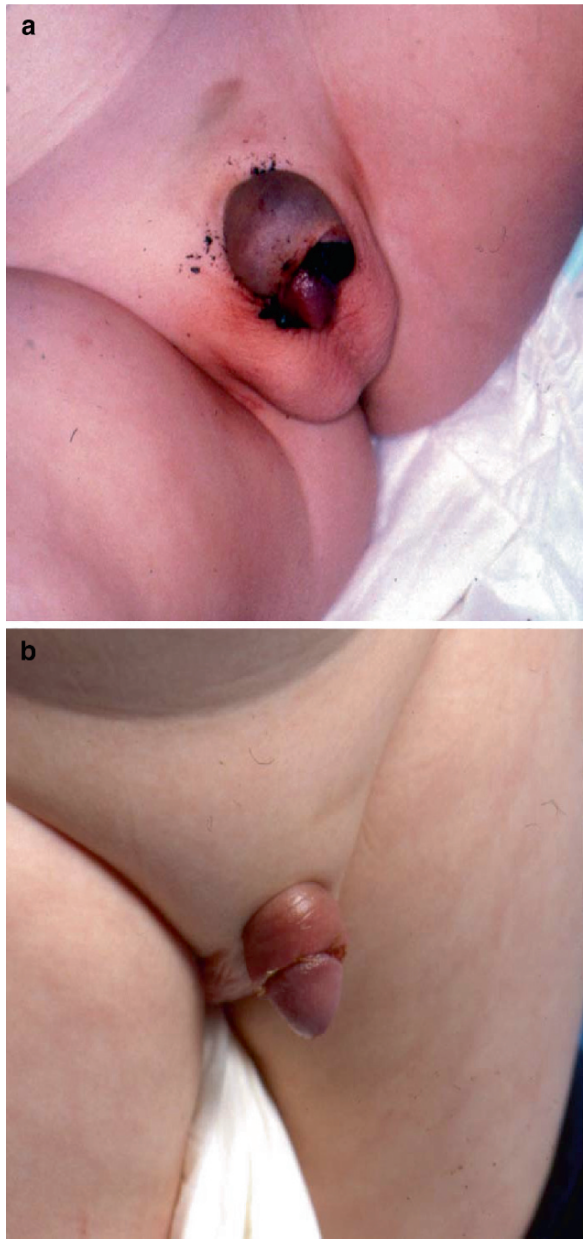

Fig. 9.3 Haemophilia A: (**a**) Post-circumcisional haematoma in an infant with no family history of haemophilia. Mutational analyses showed the presence of IVS 22 mutation. (**b**) Full haematoma resolution 1 week later following replacement with recombinant FVIII

- Recombinant factor concentrates are now the gold standard.
- Inhibitor formation to FVIII/IX is the single biggest complication in modern management of haemo-philia.

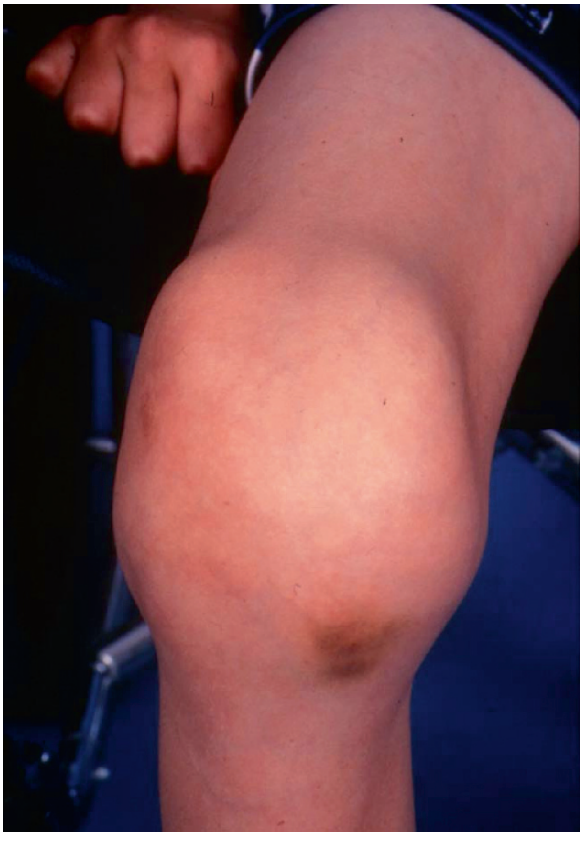

Fig. 9.4 Haemophilia B: chronic severe haemophiliac arthropathy of the right knee joint. The quadrecep muscle is severly wasted. This adolescent was only treated intermittently with plasma through out the first 5 years of life

9.2.2 Central Venous Access Devices

The intravenous administration of factor concentrate twice or three times per week is fraught with difficulty in the majority of young children when only using peripheral veins. Similarly, immune tolerance therapy (ITT) using large doses of factor concentrate, twice a day for 12–24 months for children with inhibitors to factor VIII/IX is almost impossible without regular venous access. These devices can be fully implantable (PortaCath™, Deltac USA) or partly externalised (single or double lumen Quintan™ Catheters). The use of a port is preferable to an external device because it causes fewer limitations to the child's lifestyle and it has been suggested that there is a lower infective risk. However, despite the obvious attractions of these devices, their routine use for prophylaxis and ITT has not gained universal acceptance because of the potential risks of haemorrhage, thrombosis and infection both of which may lead to a high rate of morbidity and permanent removal of the device.

Infection is cited as the reason for removal of port in up to 70% of all port removals. The rate of infection is higher in children with inhibitors. In the best of hands, the patient with a port-a-cath, without inhibitors and on regular prophylaxis, will probably have a maximum of one catheter-related infection in approximately 10 years.

There is now a growing consensus that long-term indwelling devices are necessary to facilitate the modern intensive treatment of congenital coagulation disorders. There are complications, as outlined above, in particular infections, but with improved management of the perioperative period and regular, frequent re-education, particularly in those children with inhibitors, many of these complications may be avoided.

More recently the use of arteriovenous fistulae (AVF) as a reliable means of vascular access in children with haemophilia has been reported. Complication rates are reported to be minimal: bleeding complication rate at 16%, thrombotic complication rates at 3% and infection rate at 0%. The vast majority of children (>95%) achieved functional AVF that are still regularly used for home treatment over a median period of 29 months, suggesting that this approach, i.e. the creation of AVF as the first option for achieving permanent venous access in children with severe haemophilia, is warranted.

9.2.3 Platelet Disorders

The normal range of the platelet count in fetal life is similar to that seen in adult life, being about 150–400 $\times 10^9$/l. The causes of thrombocytopenia can be divided into two broad categories: those arising on the background of an established genetic defect ((inherited thrombocytopenia) and those that are acquired either around the time of birth (congenital thrombocytopenia) or those that occur later in childhood. Inherited thrombocytopenia can be accompanied with or without dysfunctional platelets (Table 9.1). It is important to remember to confirm that the low platelet count is genuine by careful inspection of the blood sample and smear before initiating further investigations. Once

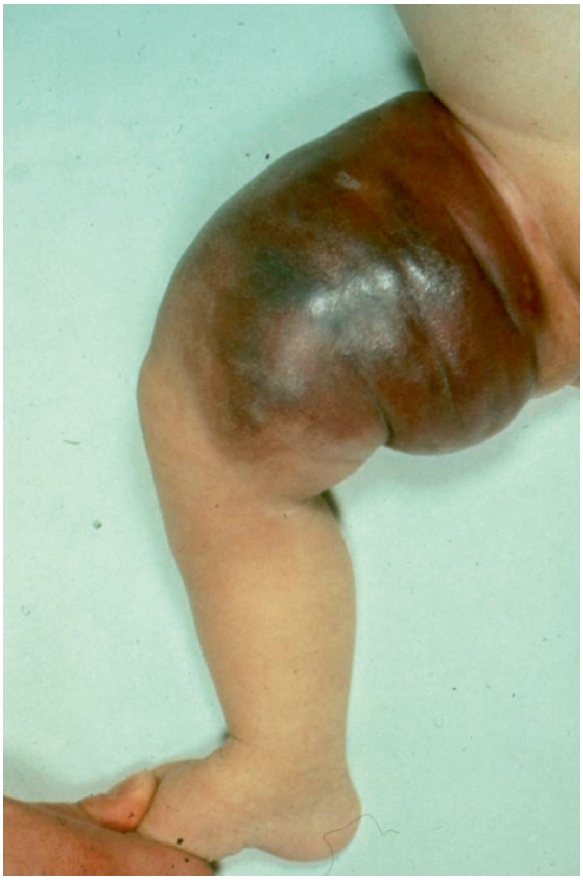

Fig. 9.5 Capillary haemangioma in a 2-month-old boy with Kasabackh-Merrit syndrome (KMS). The lesion involuted after 4 months of therapy involving vincristine, prednisilone and anti-platelet agents (asprin and ticlopidine)

established, the approach to the diagnosis of thrombocytopenia should be tailored to the individual child or infant and mother if dealing with neonatal thrombocytopenia. For example, assessment of the child's general wellbeing is very important as healthy children usually have an immune or an inherited aetiology, whereas the presence of lymphadenopathy, hepatosplenomegaly, mass lesions, hemangiomas (Fig. 9.5) bruits and congenital anomalies point towards a totally different spectrum of causes. In neonates, it should also be emphasised that obtaining a detailed maternal history, including bleeding problems, pre-eclampsia and drug ingestion in the present and past pregnancies and any history of viral infections (cytomegalovirus, rubella, herpes simplex and HIV) or connective tissue disease (systemic lupus erythematosus [SLE]), will save time and unnecessary investigation.

Immune Thrombocytopenia Purpura (ITP), defined as thrombocytopenia purpura, without any other associated condition is the commonest form seen in childhood

Clinical Features

- Predominantly seen in children aged between 2 and 5 years
- Usually preceded by a viral illness or prodrome
- Usually seen in autumn and winter months
- Bleeding uncommon when platelet count > 50,000 /ml
- Spontaneous bleeding is frequent when the platelet count < 50,000/ml
- Diagnosis is one of exclusion in that the vast majority of children will have had a preceding viral infection or will have been vaccinated in the previous month

Clinical and Patho-physiology

- Examination usually normal with the exception of cutaneous bleeding.
- Most likely a heterogenous group of disorders, whose cardinal clinical feature is a low platelet count.
- Inappropriate immune response to several different stimuli.
- The antibody produced is cross reacting to platelet surface proteins such as GPIIb–IIIa.

Treatment

- Bone marrow examination is not required in the vast majority of disorders with ITP
- The majority of children will respond spontaneously
- If treatment is required then intravenous immunoglobulin (1 g per kg for 2 days) and prednisolone (2 mg per kg daily × 7 days with taper) are front line treatments.
- Majority of children will respond but may have side-effects.
- Children who fail to respond, therapeutic interventions include anti-D, Rituximab (anti CD20) Danazol, Cyclosporin A and azathiopurine should be considered.
- A small number of children may develop a chronic form of ITP (thrombocytopenia lasting greater than 6 months) that can be symptomatic. Treatment can be problematic and hence **splenectomy** (see below) is worth considering.

9.2.4 Disseminated Intravascular Coagulopathy (DIC)

DIC is a clinico-pathological entity resulting in simultaneous and unregulated activation of the coagulation and fibrinolytic pathways. It is a syndrome of serious clinical consequences, which is encountered in all area of paediatrics particularly in the intensive care unit. DIC is not a primary disease entity; it is secondary to an underlying usually severe and most often systemic illness. DIC is a progressive, pathological process resulting in profuse thrombin formation and excessive activity of the fibrinolytic pathway and its most prominent clinical feature is a bleeding tendency.

- In DIC with haemorrhage, bleeding is typically from multiple sites, indicating the systemic nature of the process.
- Purpura fulminans seen in the majority of cases of disseminated meningococcaemia, the skin lesions appear haemorrhagic; however, microthromboses are underlying histological findings (Fig. 9.6)
- Diagnostic features in DIC include prothrombin, PT, APTT, fibrinogen, D Dimer, platelet count, blood smear and natural anticoagulant factor levels.

Treatment

- Blood product replacement in the form of FFP, cryo-precipitate, fibrinogen concentrate and platelets is the first line of therapy.
- Other forms of intervention such as heparin, natural anticoagulant concentrates and anti-fibrinolytic agents may also have a defined role.
- Since DIC is not a primary disease entity, treatment should be directed towards the underlying process causing the consumption.

9.2.5 Thrombotic Disorders

Thrombotic disease in children is rare compared to adults. When seen in childhood it is either secondary to an acquired prothrombotic state or the child has an inherited gene defect predisposing to clot formation. When it does occur in childhood it can be fatal or associated with several sequlae such as amputation, organ dysfunction and post-phlebitic syndrome. The peak incidence of these thrombotic events is undoubtedly the neonatal period.

- Thrombotic tendency is seen in a number of clinical scenarios as outlined in Tables 9.2 and 9.3.
- Approximately 80% of these genetic disorders have lesions directly or indirectly affecting the Protein C natural anticoagulant pathway (Table 9.2).
- Homozygocity of these natural anticoagulant proteins are rare, common as being Protein C deficiency that causes purpura fulminans within the neonatal period.

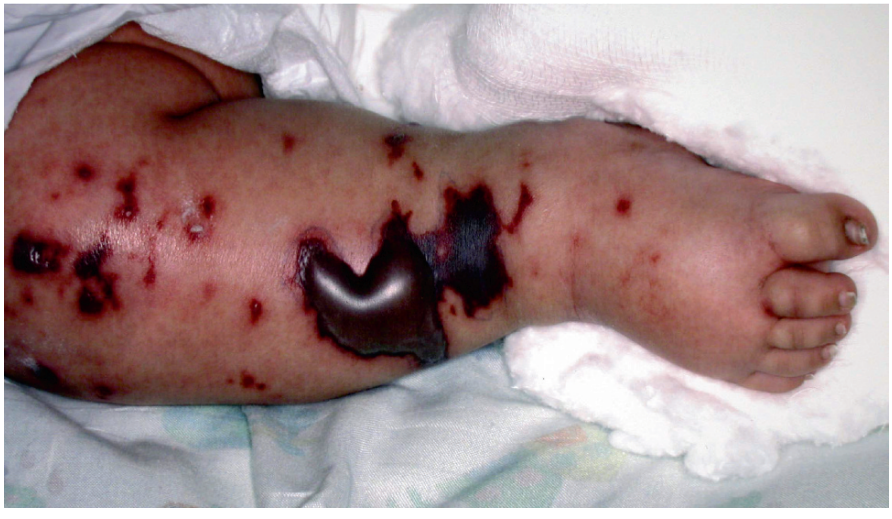

Fig. 9.6 Purpura fulminans secondary to severe acquired protein C deficiency in association with meningococcal septicaemia

Table 9.2 Acquired thrombotic tendency

- Indwelling vascular catheters
- Renal artery and vein thrombosis
- Acquired natural anticoagulant deficiency
  - Nephrotic syndrome → antithrombin deficiency
  - Purpura fulminans → varicella & protein S deficiency and meningococcaemia & protein C deficiency
- Necrotising enterocolitis (NEC)
- Respiratory distress syndrome
- Heparin-induced thrombocytopenia/thrombosis syndrome (HIT/HITTs)
- Maternal anticardiolipin antibodies (lupus anticoagulant)
- Extracorporeal membrane oxygenation (ECMO)
- Haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura (HUS / TTP)
- Birth asphyxia

Table 9.3 Inherited thrombotic tendency

- Defects within the Protein C Pathway
  - PCR and FVR506Q (factor V Leiden)
  - Protein C Deficiency
  - Protein S Deficiency
  - FIIG20210A (prothrombin gene variant)
  - High circulating levels of FVIII
- Antithrombin Deficiency
- Hyperhomocysteinaemia
  - Cystathionine B-synthase
  - Methionine synthase
  - Thermolabile methylenetetrahydrofolate reductase
- Fibrinolytic Pathway
  - PAI-1 (4G/5G polymorphic status)
  - Plasminogenaemia
- Dysfibrinogenaemia
- Haemoglobinopathy
- Platelet defects

- Heterozygotes for these natural anticoagulant deficiencies usually manifest as being venous thromboembolic disease later in life, usually in the setting where these are further perturbation to the coagulation pathway, e.g. on the background of sepsis, immobility, dehydration etc

Treatment

The indications for use of anticoagulants in infants and children have changed dramatically over the past 20 years with major advances in tertiary paediatric care such as ECMO, cardio-pulmonary bypass, haemodialysis and the use of intra-arterial and intravenous indwelling catheters. The following should be considered:

- Choice of anticoagulant is dependent on the duration of anticoagulation.
- In the acute phase, heparins, either unfractionated or low-molecular-weight forms, are used.
- In the longer term, oral anticoagulants are the treatment of choice at the present time.
- In more specific disease states such as inherited or acquired protein C or antithrombin deficiencies, factor concentrate replacement as an adjuvant haemostatic support is used increasingly.
- Children who develop heparin-induced thrombocytopenia, recombinant hirudin or a heparinoid should be considered.

9.2.6 Asplenia or Hyposplenism

The commonest form of asplenia or hyposplenism is surgical splenectomy. The usual haematological indications for splenectomy include the following:

- Repeated splenic sequestration in children with sickle cell disease
- Thalassemia major with associated hypersplenism
- Hereditary spherycytosis
- Refractory immune cytopenias

Congenital absence of the spleen can be associated with multiple abnormalities including cardiovascular and visceral abnormalities and some of these have a genetic basis.

Loss of splenic substances as a result of infarction is seen in sickle cell disease and essential thrombocytopenia, the latter being extremely rare in children. These conditions are usually accompanied by functional hyposplenism.

- Assessment of splenic filtration function is usually made by examination of the peripheral blood for evidence of red cell inclusions, which are pitted out during filtration by the normally functioning spleen (Fig. 9.7). These inclusions include Howell Jolly bodies and "pits" in red cells. The presence of Howell Jolly bodies usually reflects significant splenic hypo-function and the risk of overwhelming infection.
- Immune-mediated conditions associated with functional hyposplenism include the following:
  - Chronic graft versus host disease (GvHD)
  - HIV/AIDS
  - Coeliac disease/Dermatitis herpetiforms
  - Rheumatoid arthritis/SLE
  - Thyroid disease
  - Ulcer colitis/Crohns disease

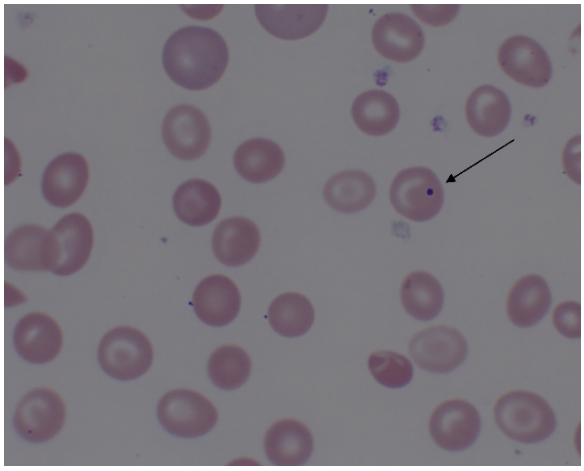

Fig. 9.7 The arrowed red cell shows a dark dense inclusion "Howell Jolly body". Howell Jolly bodies are most commonly seen in splenectomised (surgical or "auto") patients, severe forms of megaloblastic and haemolytic anaemias and haemoglobinopathies

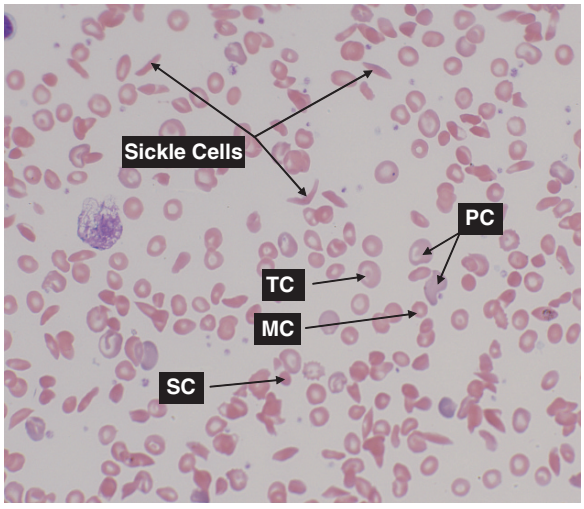

Fig. 9.8 A 9-year-old Nigerian boy with HbSS. The arrowed cells are markedly elongated with two pointed ends. Also note the other classic findings of target cells (TC), microcytes (MC), spherocytes (SC) and polychromatophilic cells (PC)

- In many of these diseases, there is not only functional hyposplenism but the spleen may also become atrophied. This is seen especially frequently in patients with coeliac disease, the majority of whom are adults.

9.2.7 Sickle Cell Disease

Sickle cell disease is common in people of African, Afro-Caribbean and Middle Eastern heritage. It is now the most common genetic disease in the UK. Sickle haemoglobin (HbS) results from a point mutation in the β-globin gene. HbS polymerises when it becomes deoxygenated, then polymerises into molecular bundles that interfere with RBC membrane structure and deformability. The distorted RBCs cannot traverse small blood vessels in the microcirculation and thus vaso-occlusion leading to ischaemia and local tissue damage occurs. The inheritance of one HbS gene ("Sickle Trait" or "HbAS") is a benign condition. Sickling disorders are seen when two HbS genes are inherited or when HbS is coinherited with certain other β-chain variants: HbC, HbE, HbD, HbO^{Arab} and β-thalassaemia. The diagnosis is suspected by blood film examination that shows characteristic sickle cells and features of hyposplenism (Fig. 9.8). It should be remembered that the "Sickledex", a solubility test is unreliable in children under 6 months old or in those who have been recently transfused. High performance liquid chromatography confirms the diagnosis and Hb electrophoresis or Isoelectric Focussing may be required if there is doubt about the nature of the abnormal Hb.

Clinical Features and Management

- Vaso-occlusion is often precipitated by cold or dehydration or infection. Causes severe pain in the affected area. Most commonly seen in bones, GIT (**may mimic acute abdomen**), lungs (may result in ARDS-type picture: "chest crisis") and brain (stroke). Priapism may also be seen.
- Pain control is essential—opiates are frequently required.
- Patients should be well hydrated and antibiotics given if there is any suspicion of infection.
- RBC transfusion (top-up or exchange) may be required for chest crisis or stroke.
- Sequestration is usually seen in the under 5-year-olds. The spleen (or liver) becomes engorged by sickled RBCs and may cause rapid haemodynamic collapse and an RBC transfusion is usually required. The parents should be instructed on how to monitor spleen size.
- Aplasia is usually seen in association with Parvovirus B19 infection (suppresses erythropoieisis). This is usually suspected with inadequate reticulocyte count.

- Sepsis is not uncommon as a significant number of these patients are hyposplenic due to autoinfarction of spleen. The most common organism is Strep. pneumoniae and is treated with broad-spectrum antibiotics.
- All patients should take prophylactic penicillin and receive Pneumovax.

With repeated vascular occlusion events, chronic complications may arise that include the following:

- Pulmonary hypertension exacerbated by chronic intravascular haemolysis causing release of free Hb and scavenging of nitric oxide.
- Nearly all patients have hyposthenuria and chronic renal impairment may be seen.
- "Silent" infarction may contribute to intellectual impairment (Fig. 9.9).
- Chronic osteomyelitis or Avascular Necrosis (AVN).
- Proliferative retinopathy is more commonly seen in HbSC disease.
- Chronic leg ulceration in young adults.

Patients are usually placed on a transfusion programme if there is evidence of acute stroke or if they have an abnormal transcranial Dopplers (flow rates in cerebral vessels are increased if vessels are narrowed due to endothelial damage—strongly predicts stroke risk). Transfusion occurs every 3–4 weeks; suppresses and iron overload should be aggressively managed with chelation therapy.

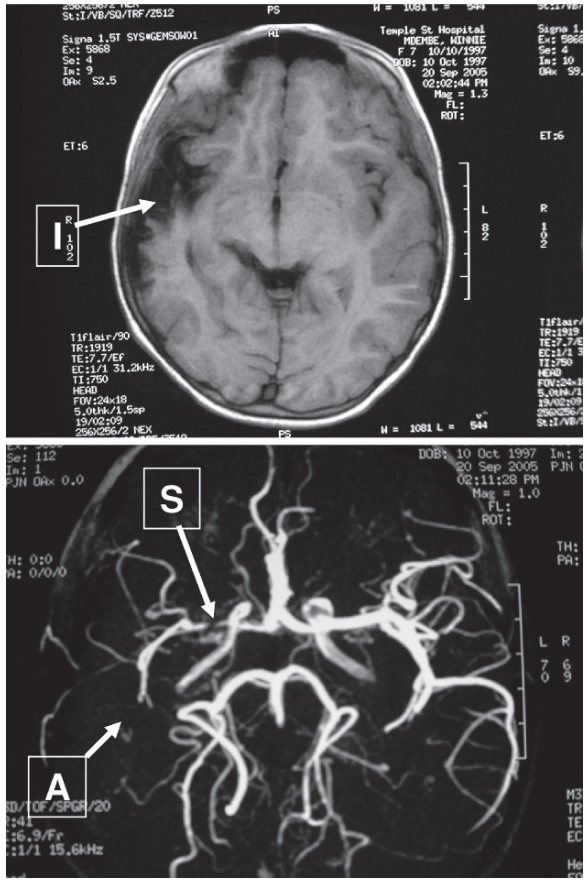

Fig. 9.9 About 25% of patients with SCD develop cerebrovascular complications and about 80 of these are under 15 years of age. The MRI Brain shows an area of infarction (I) secondary to vessel occlusion (stenosis (S) and absence (A))

9.2.8 Neutropenia and Typhilitis (Neutropenic Colitis)

9.2.8.1 Neutropenia

Neutrophils differentiate in the bone marrow for approximately 7 days and then circulate in the blood for approximately 6.5 h. Newborns often have neutrophilia for the first 2 weeks, mean count 11 × 10^9/l, whereas children between 1 month and 8 years have mean levels of 3.6 × 10^8/l. Above this age, counts are similar to adult levels.

- Neutropenia in children can have inherited or acquired causes and these are usually characterised as either transient or chronic. Sometimes the inherited neutropenia is part of a more complex syndrome (see below)
- The usual work up for a child with neutropenia requires documentation of the neutropenia over time, elimination of possible precipitating causes by history and bone marrow examination in those children in whom a clear cause is not found. Children with neutrophil counts of less than 0.5 × 10^9/l are at increased susceptibility to bacterial infections.
- Acquired transient causes include infections (viral, bacterial), burns, drugs, haemodyalisis, haematinic deficiencies (B12 Folic Acid).
- Acquired chronic causes will include haematological malignancies, myelodysplasia, immune-mediated (allo-immune and auto-immune), hypersplenism, viral, bone marrow suppression and idiopathic.
- Isolated inherited causes include infantile genetic agranulocytosis (Kostmann's Syndrome), other chronic

congenital neutropenias such as cyclical neutropenia, benign chronic neutropenia, myelokathexis
- Those associated with complex syndromes include Cartilage Hair hypoplasia, Chediak-Higashi Syndrome, Dyskerytosis Congenita, primary immuno-deficiency (e.g. S linked hyper IGM Syndrome), Fanconi Anaemia, Shwachman Diamond Syndrome, Cyclical Dysgenesis and metabolic disorders such as Glyogen Storage Type 1B Disease.
- The genetic basis for the majority of these inherited disorders has now been elucidated.
- Treatment usually involves supported measures such as antibiotics, G-CSF therapy and in those cases associated with bone marrow failure, allogeneic bone marrow transplantation.

9.2.8.2 Typhilitis (Neutropenic Colitis)

Typhilitis (inflammation of the caecum due to Gram-negative bacteria of the gut flora) is a diagnosis unique to the neutropenic patient. Its diagnosis is relatively common in the haemato-oncology wards where intensive chemotherapeutic protocols are routinely used. Patients are febrile and usually have right-sided or generalised abdominal pain. It should be remembered that no clinical findings differentiate typhilitis from other abdominal diseases. CT and ultrasound imaging show distention and thickening of the caecum and bowel wall thickening with associated marked pseudopolypoid formation of the mucosa, respectively. Neutrophil recovery is a good prognostic factor. Conservative management with broad-spectrum antibiotics and antifungals with or without bowel rest is the treatment of choice. Surgical intervention should be only be considered in the most severe cases

9.2.9 Blood Products

A list of blood products used in children in the surgical setting is shown below:

- ***Red cell concentrate*** (RBCs): Dose (ml) = (Desired rise in Hb) × 3 × recipient weight (kg)

The cross-match(ing of blood) is geared to ensure that an inadvertent exposure to a foreign antigen does not occur and consists of the following:

1. ABO and D grouping of the recipient
2. Antibody screen of the recipient (or mother in the case of neonatal transfusion)—serum is tested against a "panel" of commercially available RBCs that carry all clinically important antigens between them
3. A comparison of these results with any available historical record (a "group and screen" finishes at this point)
4. Testing of patient serum against the RBCs to be transfused

- ***Platelets***: Dose = 15 ml/kg. Usual maximum dose is one pool ("adult dose") unless bleeding or specific target platelet count
- ***Frozen Plasma*** (FP): Usual dose 15 ml/kg, usually used as source of clotting factors in DIC, haemorrhagic disease of the newborn. Children born after 01/01/96 receive "pathogen-reduced plasma", which has undergone a viral inactivation process
- ***Cryoprecipitate***: Obtained by thawing FP at 4°C, rich in fibrinogen, FVIII, VWF and FXIII. Main use is hypofibrinogenaemia (usually in DIC), usual dose 10–15 ml/kg.
- RBCs and platelets are leucodepleted to remove WBCs that can cause immune reactions and harbour infections (e.g. CMV)
- CMV negative and irradiated products are usually required for immunosuppressed patients—refer to local guidelines

There are recognised acute and long-term adverse events associated with blood product transfusions and are briefly highlighted below. The most serious reactions have similar presentations.

- Haemolytic reaction: fever, dyspnoea, back pain, haemoglobinuria (with intravascular haemolysis)
- Urticarial and anaphylactic reaction
- Bacterial contamination—usually seen with platelets (stored at 22°C)
- TRALI: Transfusion-related acute lung injury: occurs due to anti-WBC or HLA antibodies in donor or recipient. Causes ARDS-like picture
- In practice, all these possibilities need to be considered:

(i) Stop the transfusion
(ii) Assess haemodynamic stability—resuscitate if necessary

(iii) Check the patient identification against the blood product
(iv) Examine the product for abnormal appearance suggesting contamination
(v) Order full septic screen (include product if bacterial contamination is a possibility)
(vi) Order CXR if dyspnoea or hypoxia
(vii) Repeat cross-match, antibody screen and check indices of haemolysis

- Febrile non-haemolytic reaction: non-specific reaction to foreign antigen must be differentiated from more serious reactions
- Volume overload: deaths have been described in SHOT report. Must be differentiated from TRALI
- Delayed haemolytic reactions occur after 5–10 days—evidence of haemolysis and possibly renal impairment due to toxic effects of free Hb
- Infection can be bacterial, viral, protozoal (Chagas' disease), prion (vCJD Transmission reported in the UK)
- Iron overload seen with chronic RBC transfusion
- Post-transfusion purpura can occur especially in HPA-1a negative patients develop thrombocytopaenia 7–10 days post-platelet transfusion.
- Graft-versus-host disease is rare but universally fatal due to bone marrow suppression

Further Reading

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