The neurology

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Anaemia is defined by the haemoglobin concentration in peripheral blood being below the normal 14 gm/dL (SD $\pm$ 2) for women, 16 gm/dL (SD $\pm$ 2) for men and 12 gm/dL (SD $\pm$ 2) for children. The number of red blood cells is also usually reduced, below the normal $4.8 \times 10^6/\text{mm}^3$ (SD $\pm$ 0.6) for women and $5.4 \times 10^6/\text{mm}^3$ (SD $\pm$ 0.9) for men. The haematocrit is the proportion of red blood cells in the blood – normally more than 40% for men and 37% for women. The other major red blood cell indices that may be helpful in the differential diagnosis of anaemia are:

- the mean corpuscular volume (MCV), which is the average red blood cell size and is normally 87 u^3 (SD $\pm$ 5);
- the mean corpuscular haemoglobin (MCH), which is the amount of haemoglobin per cell, normally 29 pg of haemoglobin/cell (SD $\pm$ 2);
- the mean corpuscular haemoglobin concentration (MCHC), which is the average concentration of haemoglobin per cell, normally 34% (SD $\pm$ 2).

Although these indices may be useful, they are only averages and complete evaluation requires microscopic examination of the peripheral blood smear which will reveal:

- red blood cell size (macrocytosis, microcytosis) and shape, as well as their maturity (i.e. reticulocytes or nucleated cells);
- the intensity of haemoglobin staining (hypochromia, normochromia or hyperchromia)
- the presence of macrocytes, target cells, spherocytes, schistocytes or other abnormally shaped cells.

In some situations, automated analysis of the erythrocyte indices may be normal, but the peripheral blood smear shows a dimorphic

anaemia (e.g. iron deficiency plus megaloblastic anaemia). Some cells are clearly microcytic and hypochromic but others are macrocytic, accounting for the normal indices that are reflected in an automated average of the two abnormalities. No analysis of anaemia is complete without direct observation of the peripheral blood smear.

NON-SPECIFIC NEUROLOGICAL EFFECTS OF ANAEMIA

There are very few neurological effects of anaemia *per se*. Headache and lightheadedness may occur in severe anaemia but these usually require the haemoglobin concentration to be less than half of normal. In slowly developing anaemias, many patients have little or no neurological symptoms even with a haemoglobin concentration as low as one-tenth normal.

The most easily examined part of the nervous system, which reflects the effects of anaemia itself, is the eye. The reddish colour of the fundus is the result of light from the ophthalmoscope reflected back by the choroidal blood and changed to a pink colour by the pigment of the retinal epithelium. As the haemoglobin concentration falls, the reddish colour of the fundus fades.

Aside from pallor of the optic fundus, the most common ocular lesions in anaemia are retinal haemorrhages, usually small and spindle-shaped and occasionally associated with cotton wool exudates. It is believed that blood escapes from the capillaries by diapedesis and that the exudates are composed of fibrin. Both the haemorrhages and the exudates are transient. However, it is very unusual to see retinal haemorrhage when the haemoglobin concentration is greater than 50% of normal.

of anaemia

In severe anaemia (i.e. haemoglobin below 6 g/dL) a minor degree of oedema of the optic disc and adjoining retina may be observed. This is not too surprising because the oxygenation of the optic nerve head depends not only on local blood flow but also on the oxygen carrying capacity of the blood.

The retinal vessels appear to be of different calibre than normal in anaemic patients. The arteries are widened and the usual width relationship between arteries and veins of 2 : 3 approaches 1 : 1.

There have been rare reports of patients with moderately severe chronic anaemia (i.e. haemoglobin less than 10 g/dL) presenting with focal cerebral symptoms, which resolved after transfusion. Whether the symptoms reflected an unmasking of underlying previously asymptomatic, occlusive vascular disease is not clear, but focal cerebral symptomatology must be a very rare manifestation of anaemia *per se*.

IRON DEFICIENCY ANAEMIA

Iron deficiency from chronic blood loss is the most common form of anaemia. It causes a microcytic, hypochromic anaemia (Fig. 1). Iron deficiency in the *absence* of anaemia – sideropenia – can impair the deformability of red blood cells, leading to ischaemia in the territory of small cerebral vessels and resulting in a number of neurological syndromes (see below). Ferritin measurement in the blood and cerebrospinal fluid is the most effective method for diagnosing iron deficiency in non-anaemic people. This is particularly important in polycythaemia (either primary or secondary) when there are increased numbers of red blood cells, each of which may be iron deficient. Both the polycythaemia and the relative sideropenia lead to increased blood

viscosity and therefore neurological symptoms and signs.

Obsessive-compulsive disorders

Iron deficiency (usually but not always with anaemia) is associated with obsessive-compulsive behaviours, which fall into two categories:

- compulsive eating (pica);
- compulsive moving of the limbs, usually the legs (restless legs).

Common pica behaviours include eating starch, paint chips, clay (terra sigillata), earth (geophagia) and ice (pagophagia). The cause is unknown, but it cannot be an attempt to replace iron because ice eating, the most common pica behaviour, usually does nothing in this regard and many clays contain substances that actually chelate iron, thereby worsening the problem. It seems more likely that pica is some form of compulsive behaviour akin to a tic.

Figure 1 Peripheral blood smear showing the hypochromic and microcytic red blood cells typical of iron deficiency anaemia.

The restless legs syndrome is felt as an unpleasant creeping sensation deep in the legs (and occasionally in the arms) at rest. The patients feel compelled to move their legs to avoid the unpleasant feeling. Most sufferers are women, who pace the floor at night, and complain of insomnia. Polysomnographic studies often reveal nocturnal myoclonus (periodic movements of sleep). It is likely that restless legs, nocturnal myoclonus and akathisia represent various fragments of a single disorder, sometimes called Ekbom's syndrome.

Many of the movement disorders associated with iron deficiency anaemia are reminiscent of basal ganglia disorders, but their precise relationship with systemic iron deficiency is unclear. Many such patients are iron deficient, in which case the symptoms respond to iron replacement. The rest are treated with dopamine therapy (L-dopa, dopaminergic agonists). The entire Ekbom syndrome may be considered a

central nervous system dopamine deficiency syndrome separate from parkinsonism. Patients with restless legs or any other aspect of Ekbom's syndrome should have a thorough anaemia evaluation, including blood count, microscopic study of the blood smear, measurement of serum iron, total iron binding capacity, and several stool occult blood tests if they are anaemic. It should also be borne in mind that sideroopenia *may* predate any anaemia. Therefore, serum and CSF ferritin levels may be necessary in cryptic movement disorder patients if Ekbom's syndrome is a possible diagnosis.

MEGALOBLASTIC ANAEMIAS

The term megaloblastic anaemia refers to a characteristic morphological abnormality in the blood and bone marrow (Fig. 2) that probably arises from impaired DNA synthesis. This is usually the result of a deficiency of either cobalamin (vitamin B12) or folic acid, both of which are essential for the formation of the deoxyribosyl precursors of DNA. The deficiencies result in abnormal development of erythroblasts in bone marrow, which causes intramedullary haemolysis and then anaemia. The peripheral blood contains macrocytic erythrocytes (Fig. 3). The disordered DNA metabolism also affects the maturation of granulocytes, resulting in hypersegmented polymorphonuclear leucocytes in peripheral blood.

This disordered DNA metabolism is clearly not confined to the blood, because giant epithelial cells are found in many other organs including the mouth, stomach and skin. The neurological effects of the megaloblastic anaemias are probably due to a primary metabolic derangement in neural tissue, they are not directly related to the anaemia *per se*. Because the blood-forming organs are particularly sensitive to the effects of B12 or folate deficiency, it is extremely unusual to find any neurological effects in patients with completely normal blood. Some such patients have been reported, but the completeness of the haematological evaluation, or the precise nature of the neurological problem, is often unclear. These cases may have had other forms of degenerative spinal cord disease, in which the lateral and posterior columns are primarily affected, but totally unassociated with vitamin B12 deficiency. Because reliable serum B12 levels have only relatively recently been available, earlier case reports in which no haematological manifestations of B12 or folate deficiency were described must be viewed with some skepticism.

Figure 2 Smear of bone marrow to show megaloblastic red cell precursors

Figure 3 Peripheral blood smear showing macrocytosis and a hypersegmented polymorphonuclear leucocyte.

Cobalamin (vitamin B12) deficiency

This may be due to:

- defective diet (low in animal or bacterial products)
- defective absorption
 - deficiency of intrinsic factor
 - pernicious anaemia
 - gastrectomy
 - intestinal disease
 - malabsorption (sprue; resection, bypass or disease of terminal ileum)
 - blind loop syndrome
 - fish tapeworm infestation
- deranged metabolism or increased requirement (thyrotoxicosis, pregnancy, neoplasia)

Of these, the most common is pernicious anaemia, which is due to failure of the stomach to secrete adequate amounts of intrinsic factor to ensure intestinal absorption of vitamin B12 in the terminal ileum. This failure is due to atrophy of the glandular mucosa, a process that is usually an immune-mediated gastritis, but may be familial, senile or the result of gastric neoplasia. Histamine fast achlorhydria is a reliable method of diagnosing pernicious anaemia, but has been superseded by measurements of anti-intrinsic factor and antiparietal cell antibodies. Patients with auto-immune pernicious anaemia often have clinical and laboratory evidence of other conditions characterized by auto-immunity such as vitiligo and thyroiditis. Serum B₁₂ levels have occasionally been erroneously normal in documented cases so it is now routine to assess intracellular function by directly measuring serum homocysteine and methylmalonic acid.

Cobalamin (vitamin B12 or extrinsic factor) exists in two forms, methylcobalamin and adenosylcobalamin, each of which acts as an important cofactor in reactions vital to cellular function. The methylcobalamin system (Fig. 4) transfers methyl groups from methyltetrahydrofolate to homocysteine, thereby creating tetrahydrofolate, which is required for DNA synthesis, and methionine. Failure of this system results in impaired DNA synthesis and accumulation of homocysteine.

Nitrous oxide, an inhibitor of methyl transferase, causes subacute combined degeneration of the spinal cord, a fact which argues that DNA synthesis failure can cause neurological disease even though neurones are postmitotic and therefore themselves resistant to such a toxin. It is likely that this toxicity acts on oligodendrocytes, resulting in the demyelinating lesion,

which is characteristic of subacute combined degeneration. Acute exposure to nitrous oxide in the form of general anaesthesia may precipitate acute deterioration (anaesthesia paraesthesia) in patients with an otherwise mild or asymptomatic form of B12 deficiency.

The adenosylcobalamin system (Fig. 5) metabolizes propionic acid by converting methylmalonyl CoA to succinyl CoA, which then enters the Krebs cycle. Failure of this system results in an accumulation of methylmalonic acid, which is toxic to the nervous system, by promoting the formation of long-chain fatty acids with odd numbers of carbon atoms (normal long chain fatty acids, which contain even numbers of carbon atom, are formed using malonic acid). Thus, when methylmalonic acid replaces malonic acid, an extra methyl group leads to odd numbers of carbon atoms and unstable myelin.

Therefore, serum homocysteine and methylmalonic acid levels are raised when there is intracellular failure of the two cobalamin related chemical reactions, making their measurement the most accurate test for vitamin B12 deficiency.

Because vitamin B12 is stored in various tissues in large amounts, signs of any deficiency after B12 intake or absorption stops take at least 3 years to appear. Pernicious anaemia is the most common cause of cobalamin deficiency, but vitamin B12 deficiency of any cause may result in the same clinical picture. The three neu-

Figure 4 The methyl cobalamin (Cbl) dependent pathway (methyl transferase system).

Figure 5 The adenosyl cobalamin dependent pathway (propionic acid system).

rological manifestations are subacute combined degeneration of the spinal cord, mental changes and optic neuropathy.

Subacute combined degeneration of the spinal cord

Subacute combined degeneration of the spinal cord is spinal cord disease due to B12 deficiency.

Patients tend to complain of generalized weakness and paraesthesia, which usually begin distally in the upper limbs. As these symptoms progress, stiffness and weakness in the limbs develop. Loss of vibration sense is the most obvious sign, often joined later by joint position sense loss. Romberg's sign is positive and the gait is unsteady and awkward, mainly because of proprioceptive loss. Weakness and spastic-

ity are usually worse in the legs than the arms and may progress to a spastic paraplegia if untreated. Babinski signs are present, but the deep tendon reflexes are variable. They may be grossly increased with clonus, absent, or show any intermediate degree of activity. If a sensory level is found on the trunk implicating the spinothalamic tracts, this should always be viewed with great suspicion and lead one to exhaustively exclude other causes of spinal cord disease.

Most of the findings of pure vitamin B12 deficiency are attributable to myelopathy alone and there is little convincing evidence that B12 deficiency itself causes a severe neuropathy. However, in practice, the frequent concomitant existence of folate and other vitamin deficiencies makes it difficult to be sure of this point. Many patients with vitamin B12 deficiency have distal symmetrical impairment of cutaneous sensation, absent deep tendon reflexes and even slowed nerve conduction velocities suggesting a minor neuropathic component. This may be due to concomitant folate deficiency, but perhaps vitamin B12 deficiency itself causes a mild peripheral neuropathy.

Pathologically the lesion is a degeneration of white matter in the spinal cord, and occasionally the brain. These changes begin in the posterior columns of the lower cervical and upper thoracic cord segments and spread up and down, and also outwards to involve the lateral columns. The focal lesions have a rough but not absolute symmetry. This pathology can often be visualized using magnetic resonance imaging: a bright lesion can be seen on T2-weighted images (Fig. 6). Similar changes can be seen in the cerebral hemispheres and optic nerves. The myelin of peripheral nerves may also be involved but axons have not been shown to be unequivocally affected.

These pathological lesions bear a striking resemblance to those in patients infected with HIV, raising the question of whether HIV myelopathy is caused by B12 deficiency mediated by an as yet unknown mechanism.

Mental changes

Mental changes are frequent in patients with vitamin B12 deficiency: inattention, confusion, somnolence, apathy and delirium are the cardinal features. True dementia, defined as intellectual impairment in the absence of a disorder of consciousness, is a relatively rare manifestation of pure vitamin B12 deficiency. It is almost never seen without some other blood or nervous system manifestation of B12 deficiency.

Figure 6 (a) T2-weighted sagittal MR scan showing high signal (arrow) in the cervical cord in subacute combined degeneration of the cord; (b) the same lesion (arrow) in an axial MR T2-weighted scan.

Optic neuropathy

This is the third major neurological complication of vitamin B12 deficiency. There is bilateral involvement of the optic nerves, resulting in loss of central visual acuity and depressed sensitivity, greater for colour than for white in the centrocecal area of the field of vision. This is the rarest of the three neurological manifestations, but may be the only, or presenting, manifestation of B12 deficiency. It may be subclinical in many more cases than previously believed if one uses a sensitive measurement of optic nerve function such as visual evoked responses. This syndrome is clinically similar to a number of other bilateral optic neuropathy syndromes, including so-called tobacco-alcohol amblyopia, diabetic optic neuritis, Leber's hereditary optic atrophy and tropical ataxic neuropathy. Some feel that the aetiology of all of these syndromes, including vitamin B12 deficiency optic neuropathy, is linked to an abnormality of cyanide metabolism due to a shortage of sulphur donating amino acids.

Folic acid (folate) deficiency

Folate deficiency accounts for nearly all the cases of megaloblastic anaemia not due to vitamin B12 deficiency. The causes are:

- defective diet (low in vegetables and liver)
- defective absorption
 - intestinal malabsorption (sprue; steatorrhoea; massive diverticulosis; short circuits of the gastrointestinal tract)
 - blind loop syndrome
- deranged metabolism
 - increased requirement (haemolytic anaemia, pregnancy, neoplasia)
 - impaired utilization (liver disease, administration of folic acid antagonists or anti-convulsants).

Unlike vitamin B12, the body stores of folic acid are very limited so a folate deficiency syndrome may start within a few months of dietary deprivation, making it a much more common problem among the malnourished than vitamin B12 deficiency.

Folate, after being absorbed through the entire small intestine, is reduced by specific liver enzymes to tetrahydrofolic acid, a compound that plays a major role in the metabolism of one-carbon fragments by its synthesis and transfer of methyl groups. Via this mechanism, folate is vital for the conversion of deoxyuridate to thymidylate, a precursor needed for DNA synthesis. Thus, tetrahydrofolate derivations

are closely linked to vitamin B12 dependent reactions, and the haematological alterations in vitamin B12 and folate deficiency are indistinguishable. Deficiencies of the two vitamins have very similar effects and a deficiency of one may lead to faulty utilization of the other. For example, patients with vitamin B12 deficiency may have a raised serum folate, which rapidly plummets when vitamin B12 is administered, thus requiring concomitant treatment with folate lest a folate deficiency state, previously masked by the vitamin B12 deficiency, should become clinically significant. Whilst many patients with vitamin B12 deficiency have concomitant folate deficiency, the vast majority of those with the overwhelmingly more common folate deficiency have no vitamin B12 deficiency.

Folic acid deficiency is almost never pure. Because it is caused by malnutrition it is nearly always associated with multiple vitamin deficiencies. The most common neurological manifestation of this multivitamin deficiency state is a polyneuropathy, but dementia, depression and gait disorder in the elderly may be related to concomitant folate and B12 deficiency due to age related (nonautoimmune) gastric atrophy. It should be borne in mind that folate replacement may mask the effects of B12 deficiency in rapidly turning over cell populations (e.g. bone marrow or gastrointestinal tract) while permitting and perhaps even accelerating the neurological effects of B12 deficiency.

The symptomatology of nutritional polyneuropathy includes distal paraesthesia, burning and weakness. On examination, there is distal loss of reflexes and sensation. The essential pathological change is 'dying-back' axonal degeneration. Some minor degree of segmental demyelination may also occur, usually due to entrapment of metabolically weakened nerves. The common entrapment neuropathies (e.g. carpal tunnel syndrome, meralgia paraesthetica, peroneal palsy or ulnar palsy) are all more frequent in patients with an underlying metabolic axonopathy such as that due to vitamin deficiency.

In circumstances in which the major vitamin deficiency is likely to be folic acid (i.e. when folate antagonists have been given), a mild polyneuropathy of the type described above occurs. But even in these patients, the concomitant existence of other vitamin deficiencies and/or neurotoxic substances cannot be rigorously excluded. There is no evidence that pure folate deficiency has any other neurological manifestations.

HAEMOGLOBINOPATHIES AND THALASSAEMIA

Haemoglobin consists of four coiled polypeptide chains of two varieties, so that two of each type are present. There are four normal polypeptide sequences designated alpha, beta, gamma and delta. Haemoglobin A consists of two alpha and two beta chains designated $\alpha_2\beta_2$. HbA₂ consists of $\alpha_2\delta_2$ and HbF consists of $\alpha_2\gamma_2$. Disorders in which a structurally abnormal haemoglobin is considered to play a primary pathological role are referred to as haemoglobinopathies. Alterations in the *proportions* of normal forms of haemoglobin are designated by individual terms, such as thalassaemia.

Several mechanisms result in abnormal haemoglobin. A single amino acid substitution may occur in one of the two pairs of polypeptide chains. Other abnormal haemoglobins result from cross-over of the adjacent structural genes for the beta, gamma and delta polypeptides. Haemoglobins consisting of a single variety of polypeptide rather than the normal two have been described, and abnormalities resulting in the switch from foetal to adult haemoglobin are known. Finally, abnormalities in the mechanism controlling the rate of release or synthesis of various polypeptide chains are thought to result in the thalassemia group of disorders.

Most abnormal haemoglobins cause no haematological problem. However, some diseases are directly attributable to changes in haemoglobin structure, which leads to a variety of steric changes in the molecule. Sick cell haemoglobin forms insoluble polymers when deoxygenated and the HbM variants lead to excessive levels of methaemoglobin. HgM combines irrevers-

ibly with oxygen while other types such as HbQ are easily denatured and precipitate within the erythrocytes to form Heinz bodies.

A person homozygous for a structural mutation involving one of the polypeptide chains of HbA will produce only a single abnormal adult variety of haemoglobin; there are three examples, HbS, HbC, and HbE. Of these, the most important is HbS, which causes sickle cell anaemia. HbC and HbE diseases are generally mild and have no known neurological complications.

Sickle cell anaemia (HbS disease)

Most of the manifestations of sickle cell anaemia are related to the characteristic property of HbS to crystallize under conditions of reduced oxygen tension. This leads to sickled erythrocytes (Fig. 7) becoming trapped in terminal arterioles and capillaries, which results in more hypoxia, increased sickling, thrombosis and infarction. Tissues that normally contain blood at low oxygen tensions, such as the renal medulla and pulmonary arterioles, are at greatest risk, but sickling may also occur in other organs including the relatively well-oxygenated brain and spinal cord. Haemolysis results largely from the fact that the sickled erythrocytes are rigid, less flexible and more fragile than normal cells. The neurological complications of sickle cell anaemia may be divided into four categories: painful crises, vascular disease, infection and fat embolism.

Painful crises are one of the most common clinical problems. The abdominal and bone pains so common in this disease are probably due to ischaemia related to the sickling phenomenon described above.

Vascular disease is the most serious neurological aspect of this disorder and probably contributes in a major way to the decreased life expectancy of patients with sickle cell anaemia. Among children with stroke under the age of 15 years, sickle cell anaemia is present in 7%, making it an important cause of stroke in childhood. The overall prevalence of strokes in sickle cell anaemia is about 20%, obviously a massive increase over other people of similar age. Most of the strokes are due to small vessel occlusions, often resulting in seizures at the onset of the stroke. Rupture of these fragile vessels can lead to intracerebral, subarachnoid, spinal and retinal haemorrhagic strokes. Large vessel occlusions have also been reported, the supraclinoid carotid artery being a site of pre-

Figure 7 Peripheral blood smear showing sickled red blood cells

deliction (Fig. 8). The cause is unclear. Some believe that a hyperdynamic circulation leads to endothelial damage. Others hold that chronic stasis leads to thrombosis, while others have postulated that sickled erythrocytes occlude the vasa vasorum of large vessels which causes ischaemic damage to the vessel wall leading to thrombosis. Whatever the exact mechanism, the progressive stenosis of the supraclinoid internal carotid artery, which can be detected by transcranial Doppler ultrasound, can lead to the moya–moya syndrome. Spinal cord infarction is also seen, and much more prevalent than in the general population.

Sepsis is the most common cause of death in patients with sickle cell anaemia and bacterial infection accounts for as many as one half of all hospitalizations in these patients. Meningitis is particularly important, causing 20% of the deaths from sepsis. Some older children and adults with meningitis have been reported but most of the patients are infants. *Streptococcus pneumoniae* is an unusually common organism in these patients – accounting for about three-quarters of the cases of meningitis – most of whom are under 3 years old. They have a peculiarly malignant course, often leading to death within a few hours. Recurrent meningitis also seems to be common. Other children in this age group tend to have *Haemophilus influenza* type B as the leading cause of meningitis.

The unusual susceptibility of patients with sickle cell anaemia to infection is not totally understood, but important factors include their functional asplenia, and an opsonizing defect that causes leucocyte malfunction.

Fat embolism in sickle cell anaemia is more frequent than expected and the brain is involved in more than 80% of the patients in whom it is examined. Bone pain, fever, and changes in mental status are the major presenting features.

Heterozygous haemoglobin states and complex haemoglobin combinations

Sickle cell trait is occasionally associated with neurological complications, especially when patients at risk are exposed to an extremely low oxygen tension (e.g. high altitude flying, anaesthesia).

The HbSC; HbSD; HbSF; and HbS–thalassaemia syndromes are all situations in which there is a risk of neurological complications similar to those mentioned above for homozygous HbS disease. However, there are

fewer neurological problems in these combined haemoglobin disorders than in pure sickle cell disease.

Thalassemia

There are two major forms of thalassaemia, one with defective alpha chain synthesis, the other with defective beta chain synthesis. The more common beta-thalassaemia may occur in heterozygous or homozygous forms to produce the syndromes of thalassaemia trait and Cooley's anaemia (thalassaemia major), respectively. Heterozygosity for alpha thalassaemia results in a very mild condition and may require an associated haemoglobin abnormality for clinical expression (thalassaemia minor). Homozygous alpha thalassaemia is thought to be incompatible with normal foetal development.

The neurological complications in the thalassaemias may be divided into two distinct categories: meningitis following splenectomy to control haemolysis (discussed above under sickle cell anaemia), and spinal cord and/or brain compression due to extramedullary haematopoiesis.

Extramedullary haematopoiesis in the presence of a haemolytic anaemia is believed to be a compensatory mechanism by totipotent cells in various locations, usually in parts of the reticuloendothelial system, particularly the liver, spleen and lymph nodes. However, the spinal extradural space (Figs 9 and 10), and rarely the intracranial subdural space (Figs 11 and 12), may be involved with compression of the spinal cord and/or brain. About one third of patients with myelopathy due to extramedullary haematopoiesis have thalassaemia as the underlying disease. Nearly all the spinal cases involve the thoracic segments posteriorly, usually over multiple levels.

Figure 8 Lateral view of selective catheter carotid angiogram showing supraclinoid stenosis of the internal carotid artery and the moya–moya syndrome in sickle cell anaemia.

Figure 9 Postmortem specimen showing extramedullary haematopoiesis in the spinal extradural space (arrow).

Figure 11 Postmortem specimen showing extra medullary haematopoiesis in the subdural space adjacent to the clivus.

Figure 10 Sagittal MR scan showing extra medullary haematopoiesis in the spinal extradural space (arrow).

Figure 12 Axial MR scan showing extra medullary haematopoiesis on the clivus (arrow).

THROMBOTIC THROMBOCYTOPENIC PURPURA (MOSCHCOWITZ DISEASE)

This is usually defined as the triad of thrombocytopenic purpura, haemolytic anaemia and neurological manifestations. Fever and renal impairment are also almost invariable. The diagnosis requires histological demonstration of the characteristic pathological lesion: widespread hyaline occlusion of terminal arterioles and capillaries (Fig. 13). This can be accomplished from many tissues, the most accessible of which are lymph node, bone marrow, skin and spleen. The blood smear often shows a microangio-

pathic haemolytic anaemia (Fig. 14). The most important pathological changes in the nervous system are a striking increase in the cellularity of the walls of arterioles and capillaries, with platelet thrombi associated with multiple small foci of parenchymal necrosis and petechial haemorrhages (Figs 15 and 16). Grey matter is affected more than white matter. These changes are identical to those seen in other organs and are part of the systemic disease.

The neurological manifestations reflect the widespread grey matter involvement. The most common are: headache, mental change including altered states of consciousness, agitation, confusion, delirium, hemiparesis, aphasia,

syncope, visual changes, dysarthria, seizures, coma, cranial nerve palsies, paraesthesia and vertigo.

The pathogenesis is obscure. Many theories have been put forward, such as, toxins, drug sensitivity, bacterial infections, autoimmune reactions, collagen disease etc. At present most favour immunologically mediated endothelial injury. The disorder has occurred in association with an immune response (triggered by vaccination or infection) and in the course of certain autoimmune diseases such as systemic lupus erythematosus.

The haemolytic uraemic syndrome, a childhood disorder similar in many respects to thrombotic thrombocytopenic purpura, may also be triggered by immune complexes. The same can be said of the HELLP syndrome seen in the peripartum period (haemolytic anaemia, elevated liver function tests, low platelets).

FURTHER READING

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Figure 13 Small vessel occlusion in thrombotic thrombocytopenic purpura (H and E stain).

Figure 14 Peripheral blood smear showing the microangiopathic haemolytic changes of thrombotic thrombocytopenic purpura.

Figure 15 Postmortem brain, coronal cut, showing widespread and severe purpuric lesions in thrombotic thrombocytopenic purpura.

Figure 16 Postmortem brain showing mamillary body haemorrhagic lesions in a patient with thrombotic thrombocytopenic purpura.